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(12) **United States Patent**
Dalla-Favera

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(45) **Date of Patent: Jan. 4, 2011**

(54) **ISOLATION OF FIVE NOVEL GENES CODING FOR NEW FC RECEPTORS-TYPE MELANOMA INVOLVED IN THE PATHOGENESIS OF LYMPHOMA/MELANOMA**

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(51) **Int. Cl.**

C07K 1/00	(2006.01)
C07K 14/00	(2006.01)
C07K 16/00	(2006.01)
C07K 17/00	(2006.01)
C07K 17/14	(2006.01)
A61K 35/14	(2006.01)
A61K 38/16	(2006.01)
C12P 21/08	(2006.01)

(52) **U.S. Cl.** **530/387.9**; 530/350; 530/380; 530/386; 530/387.1; 530/387.3; 530/387.7; 530/388.1; 530/388.15; 530/391.1; 530/391.3; 530/391.7

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner—Alana M Harris
(74) *Attorney, Agent, or Firm*—John P. White; Cooper & Dunham LLP

(57) **ABSTRACT**

This invention provides an isolated nucleic acid molecule which encodes immunoglobulin receptor, Immunoglobulin superfamily Receptor Translocation Associated, IRTA, protein. Provided too, are the IRTA proteins encoded by the isolated nucleic acid molecules, IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 proteins, having the amino acid sequences set forth in any of FIG. **18**A, **18**B-**1**-**18**B-**3**, **18**C-**1**-**18**C-**2**, **18**D-**1**-**18**D-**2** or **18**E-**1**-**18**E-**2**. Oligonucleotides of the isolated nucleic acid molecules are provided. Antibodies directed to an epitope of a purified IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 proteins are also provided, as are pharmaceutical compositions comprising such antibodies or oligonucleotides. Methods for detecting a B cell malignancy in a sample from a subject; diagnosing B cell malignancy in a sample from a subject; detecting human IRTA protein in a sample; and treating a subject having a B cell cancer are also provided.

16 Claims, 34 Drawing Sheets

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FIGURE 1

FIG.1A

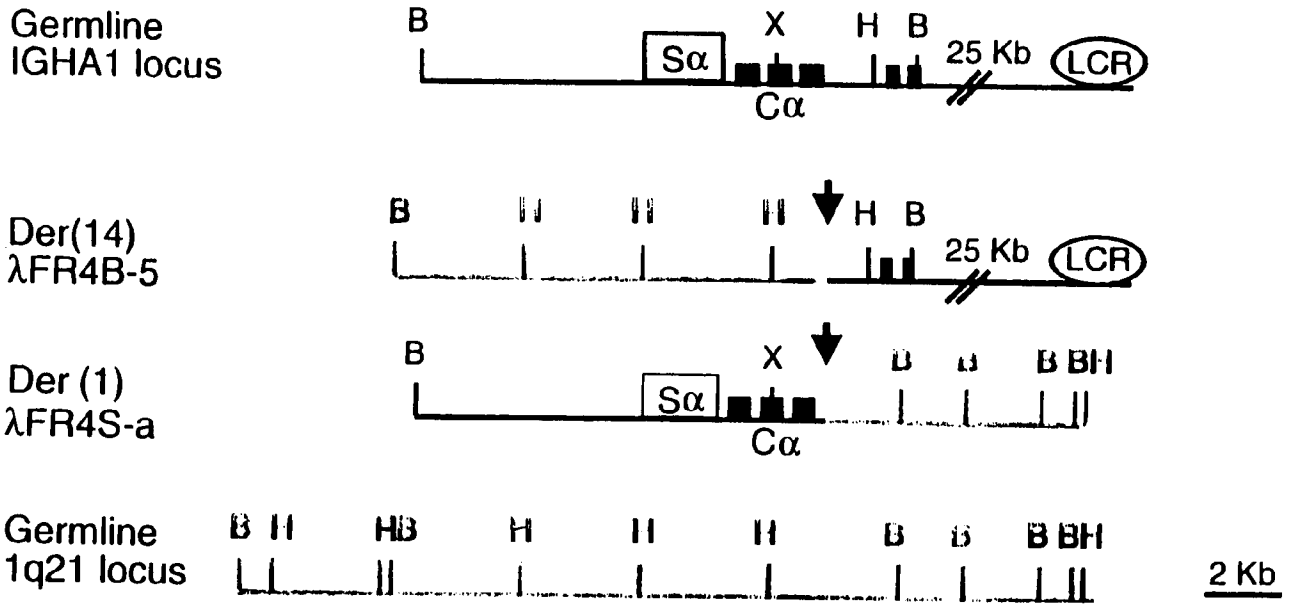
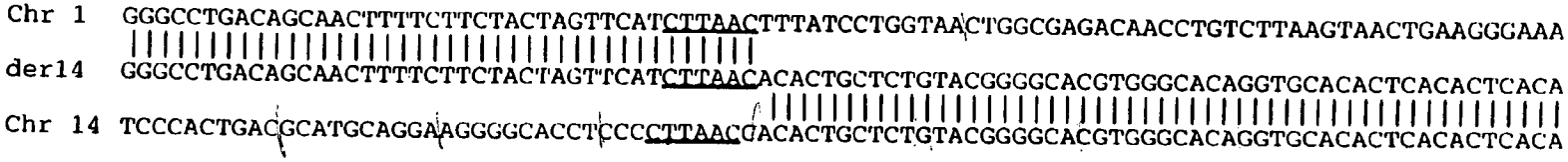


FIG.1B



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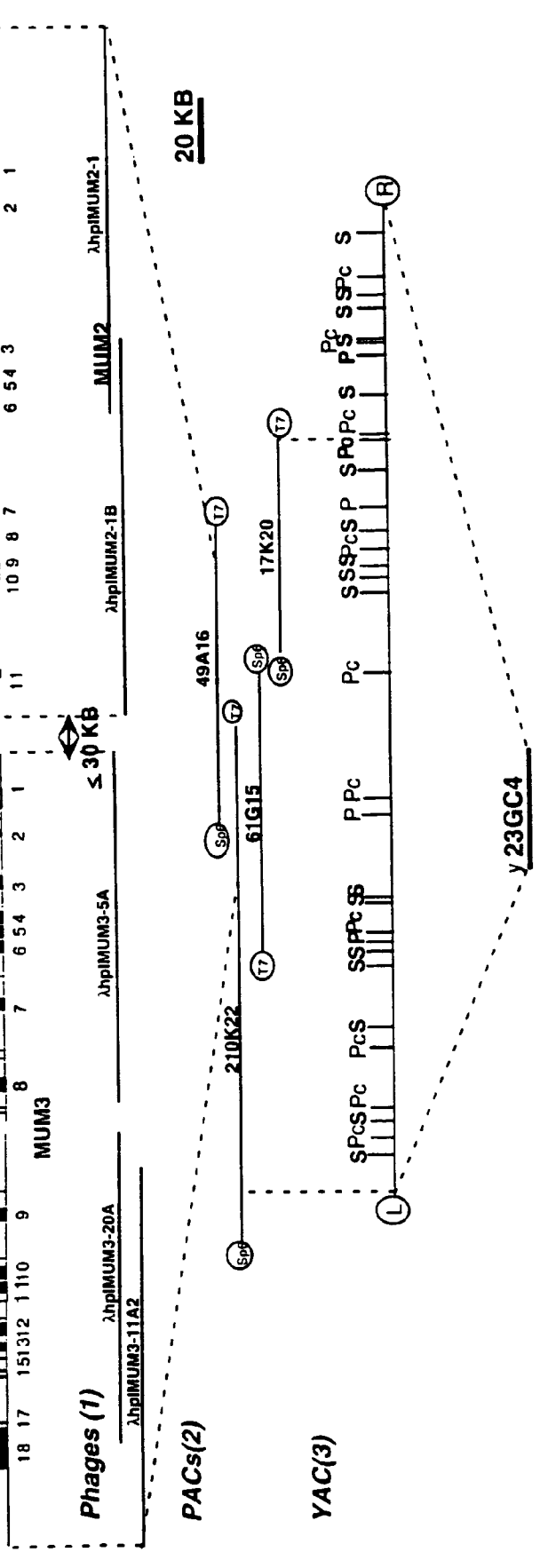
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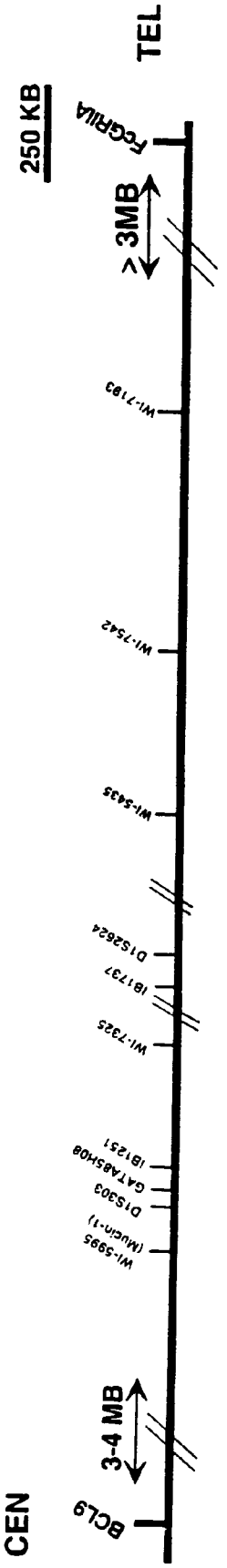
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FIGURE 2B

FIGURE 3

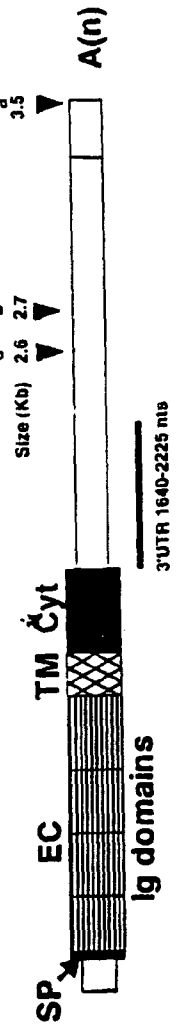


FIG. 3A

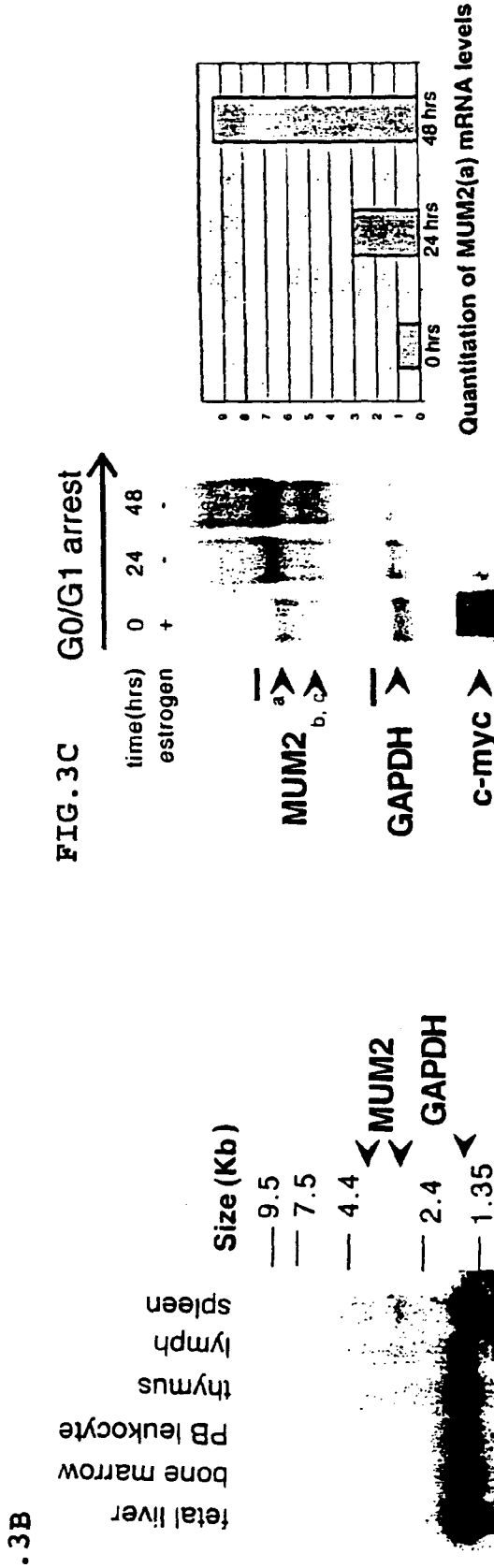


FIG. 3B

FIG. 3C

FIGURE 4

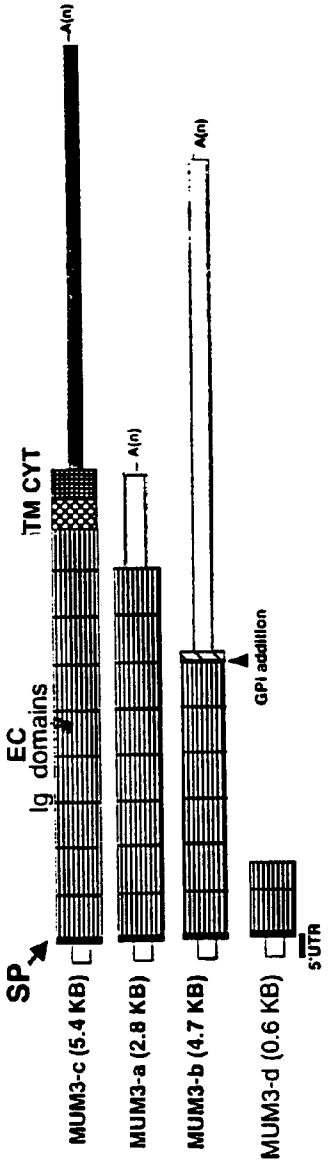


FIG. 4A

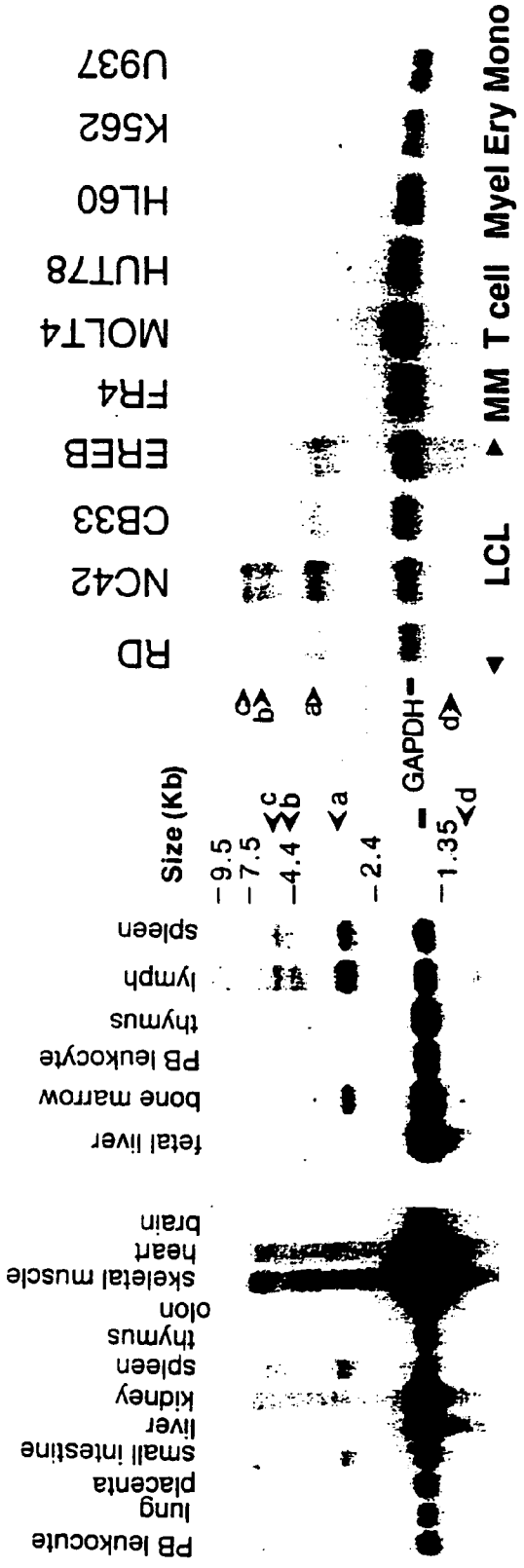
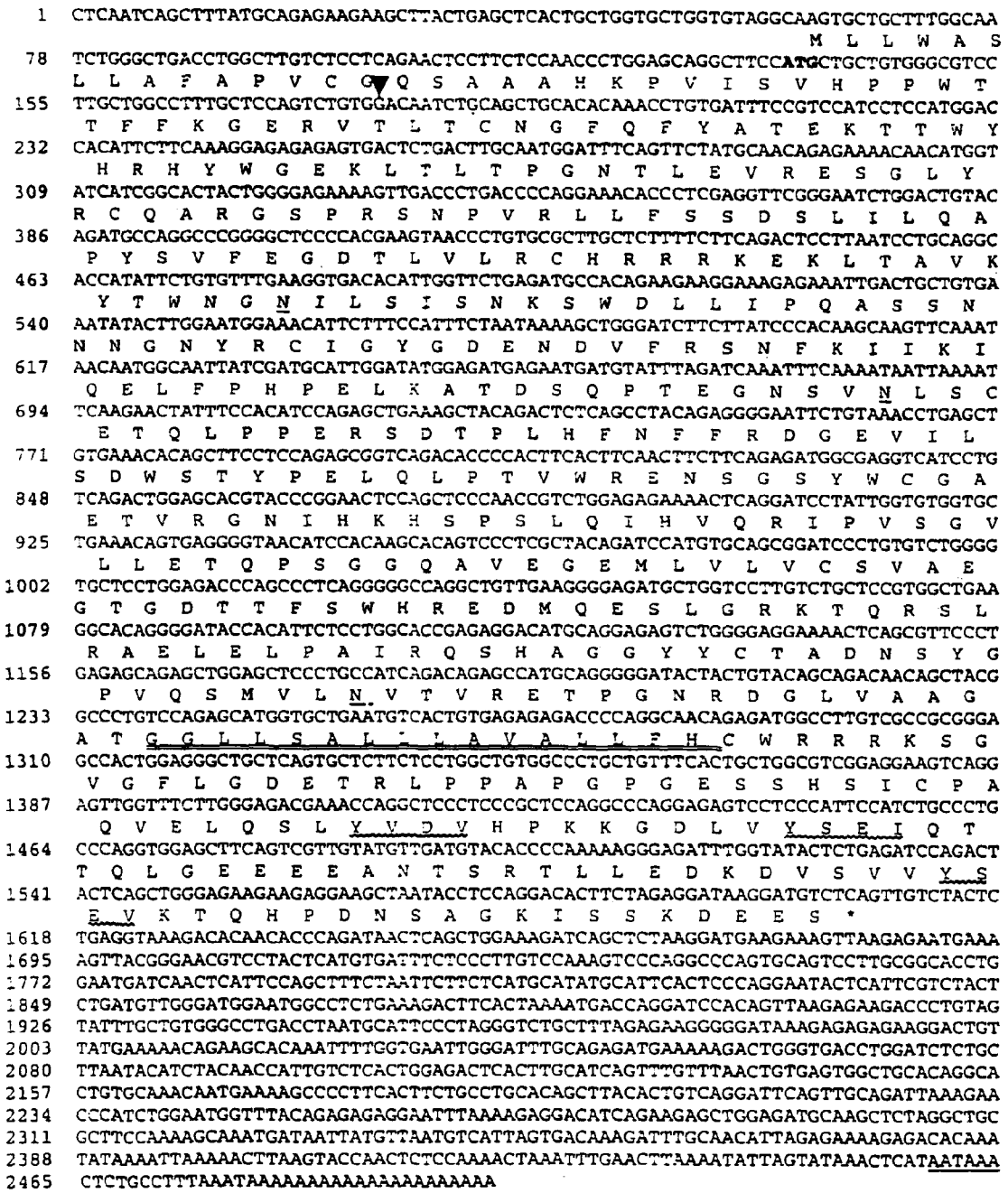


FIG. 4B

FIGURE 5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G T G D T T F S W H R E D M Q E S L G R K T Q R S L 340
1079 GGCACAGGGGATACCACATTCTCCTGGCACCGAGAGGACATGCAGGAGAGTCTGGGGAGGAAAACTCAGCGTTCCCT
R A E L E L P A I R Q S H A G G Y Y C T A D N S Y G 366
1156 GAGAGCAGAGCTGGAGCTCCCTGCCATCAGACAGAGCCATGCAGGGGGATACTACTGTACAGCAGACAACAGCTACG
P V Q S M V L N V T V R E T P G N R D G L V A A G 391
1233 GCCCTGTCCAGAGCATGGTGCTGAATGTCACTGTGAGAGAGACCCCAGGCAACAGAGATGGCCTTGTCGCCGCGGGA
A T G G L L S A L I L A V A L L F H C W R R R K S G 417
1310 GCCACTGGAGGGCTGCTCAGTGCTCTTCTCCTGGCTGTGGCCCTGCTGTTTCACTGCTGGCGTCGGAGGAAGTCAGG
V G F L G D E T R L P P A P G P G E S S H S I C P A 443
1387 AGTTGGTTTCTTGGGAGACGAAACCAGGCTCCCTCCCGCTCCAGGCCCAGGAGAGTCCTCCCATTCCATCTGCCCTG
Q V E L Q S L Y V D V H P K K G D L V Y S E I Q T 468
1464 CCCAGGTGGAGCTTCAGTCGTTGTATGTTGATGTACACCCCAAAAAGGGAGATTTGGTATACTCTGAGATCCAGACT
T Q L G E E E E A N T S R T L L E D K D V S V V Y S 494
1541 ACTCAGCTGGGAGAAGAAGAGGAAGCTAATACCTCCAGGACACTTCTAGAGGATAAGGATGTCTCAGTTGTCTACTC
E V K T Q H P D N S A G K I S S K D E E S * 515
1618 TGAGGTAAAGACACAACACCCAGATAACTCAGCTGGAAAGATCAGCTCTAAGGATGAAGAAAGTTAAGAGAATGAAA
1695 AGTTACGGGAACGTCCTACTCATGTGATTTCTCCCTTGTCCAAAGTCCCAGGCCCAGTGCAGTCCTTGCGGCACCTG
1772 GAATGATCAACTCATTCCAGCTTTCTAATTCTTCTCATGCATATGCATTCACTCCCAGGAATACTCATTCGTCTACT
1849 CTGATGTTGGGATGGAATGGCCTCTGAAAGACTTCACTAAAATGACCAGGATCCACAGTTAAGAGAAGACCCTGTAG
1926 TATTTGCTGTGGGCCTGACCTAATGCATTCCCTAGGGTCTGCTTTAGAGAAGGGGGATAAAGAGAGAGAAGGACTGT
2003 TATGAAAAACAGAAGCACAAATTTTGGTGAATTGGGATTTGCAGAGATGAAAAAGACTGGGTGACCTGGATCTCTGC
2080 TTAATACATCTACAACCATTGTCTCACTGGAGACTCACTTGCATCAGTTTGTTTAACTGTGAGTGGCTGCACAGGCA
2157 CTGTGCAAACAATGAAAAGCCCCTTCACTTCTGCCTGCACAGCTTACACTGTCAGGATTCAGTTGCAGATTAAAGAA
2234 CCCATCTGGAATGGTTTACAGAGAGAGGAATTTAAAAGAGGACATCAGAAGAGCTGGAGATGCAAGCTCTAGGCTGC
2311 GCTTCCAAAAGCAAATGATAATTATGTTAATGTCATTAGTGACAAAGATTTGCAACATTAGAGAAAAGAGACACAAA
2388 TATAAAATTAAAAACTTAAGTACCAACTCTCCAAAACTAAATTTGAACTTAAAATATTAGTATAAACTCATAATAAA
2465 CTCTGCCTTTAAATAAAAAAAAAAAAAAAAAAAAA

FIGURE 6a

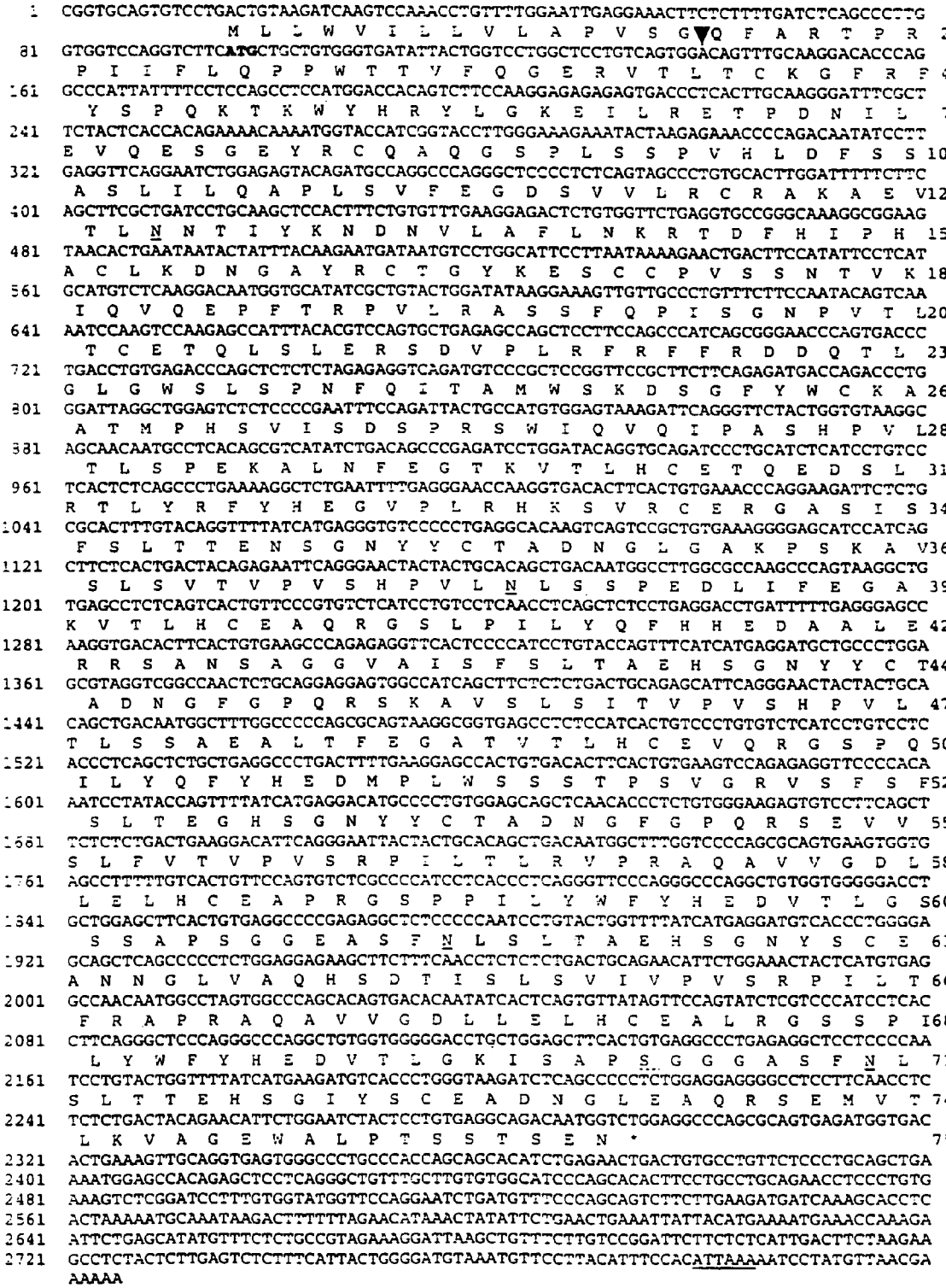

1 CGGTGCAGTGTCCTGACTGTAAGATCAAGTCCAAACCTGTTTTGGAATTGAGGAAACTTCTCTTTTGATCTCAGCCCTTG
M L L W V I L L V L A P V S G Q F A R T P R 22
81 GTGGTCCAGGTCTTCATGCTGCTGTGGGTGATATTACTGGTCCTGGCTCCTGTCAGTGGACAGTTTGCAAGGACACCCAG
P I I F L Q P P W T T V F Q G E R V T L T C K G F R P 49
161 GCCCATTATTTTCCTCCAGCCTCCATGGACCACAGTCTTCCAAGGAGAGAGAGTGACCCTCACTTGCAAGGGATTTCGCT
Y S P Q K T K W Y H R Y L G K E I L R E T P D N I L 75
241 TCTACTCACCACAGAAAACAAAATGGTACCATCGGTACCTTGGGAAAGAAATACTAAGAGAAACCCCAGACAATATCCTT
E V Q E S G E Y R C Q A Q G S P L S S P V H L D F S S 102
321 GAGGTTCAGGAATCTGGAGAGTACAGATGCCAGGCCCAGGGCTCCCCTCTCAGTAGCCCTGTGCACTTGGATTTTTCTTC
A S L I L Q A P L S V F E G D S V V L R C R A K A E V129
401 AGCTTCGCTGATCCTGCAAGCTCCACTTTCTGTGTTTGAAGGAGACTCTGTGGTTCTGAGGTGCCGGGCAAAGGCGGAAG
T L N N T I Y K N D N V L A F L N K R T D F H I P H 155
481 TAACACTGAATAATACTATTTACAAGAATGATAATGTCCTGGCATTCCTTAATAAAAGAACTGACTTCCATATTCCTCAT
A C L K D N G A Y R C T G Y K E S C C P V S S N T V K 182
561 GCATGTCTCAAGGACAATGGTGCATATCGCTGTACTGGATATAAGGAAAGTTGTTGCCCTGTTTCTTCCAATACAGTCAA
I Q V Q E P F T R P V L R A S S F Q P I S G N P V T L209
641 AATCCAAGTCCAAGAGCCATTTACACGTCCAGTGCTGAGAGCCAGCTCCTTCCAGCCCATCAGCGGGAACCCAGTGACCC
T C E T Q L S L E R S D V P L R F R F F R D D Q T L 235
721 TGACCTGTGAGACCCAGCTCTCTCTAGAGAGGTCAGATGTCCCGCTCCGGTTCCGCTTCTTCAGAGATGACCAGACCCTG
G L G W S L S P N F Q I T A M W S K D S G F Y W C K A 262
801 GGATTAGGCTGGAGTCTCTCCCCGAATTTCCAGATTACTGCCATGTGGAGTAAAGATTCAGGGTTCTACTGGTGTAAGGC
A T M P H S V I S D S P R S W I Q V Q I P A S H P V L289
881 AGCAACAATGCCTCACAGCGTCATATCTGACAGCCCGAGATCCTGGATACAGGTGCAGATCCCTGCATCTCATCCTGTCC
T L S P E K A L N F E G T K V T L H C E T Q E D S L 315
961 TCACTCTCAGCCCTGAAAAGGCTCTGAATTTTGAGGGAACCAAGGTGACACTTCACTGTGAAACCCAGGAAGATTCTCTG
R T L Y R F Y H E G V P L R H K S V R C E R G A S I S 342
1041 CGCACTTTGTACAGGTTTTATCATGAGGGTGTCCCCCTGAGGCACAAGTCAGTCCGCTGTGAAAGGGGAGCATCCATCAG
F S L T T E N S G N Y Y C T A D N G L G A K P S K A V369
1121 CTTCTCACTGACTACAGAGAATTCAGGGAACTACTACTGCACAGCTGACAATGGCCTTGGCGCCAAGCCCAGTAAGGCTG
S L S V T V P V S H P V L N L S S P E D L I F E G A 395
1201 TGAGCCTCTCAGTCACTGTTCCCGTGTCTCATCCTGTCCTCAACCTCAGCTCTCCTGAGGACCTGATTTTTGAGGGAGCC
K V T L H C E A Q R G S L P I L Y Q F H H E D A A L E 422
1281 AAGGTGACACTTCACTGTGAAGCCCAGAGAGGTTCACTCCCCATCCTGTACCAGTTTCATCATGAGGATGCTGCCCTGGA
R R S A N S A G G V A I S F S L T A E H S G N Y Y C T449
1361 GCGTAGGTCGGCCAACTCTGCAGGAGGAGTGGCCATCAGCTTCTCTCTGACTGCAGAGCATTCAGGGAACTACTACTGCA
A D N G F G P Q R S K A V S L S I T V P V S H P V L 475
1441 CAGCTGACAATGGCTTTGGCCCCCAGCGCAGTAAGGCGGTGAGCCTCTCCATCACTGTCCCTGTGTCTCATCCTGTCCTC
T L S S A E A L T F E G A T V T L H C E V Q R G S P Q 502
1521 ACCCTCAGCTCTGCTGAGGCCCTGACTTTTGAAGGAGCCACTGTGACACTTCACTGTGAAGTCCAGAGAGGTTCCCCACA
I L Y Q F Y H E D M P L W S S S T P S V G R V S F S F529
1601 AATCCTATACCAGTTTTATCATGAGGACATGCCCCTGTGGAGCAGCTCAACACCCTCTGTGGGAAGAGTGTCCTTCAGCT
S L T E G H S G N Y Y C T A D N G F G P Q R S E V V 555
1681 TCTCTCTGACTGAAGGACATTCAGGGAATTACTACTGCACAGCTGACAATGGCTTTGGTCCCCAGCGCAGTGAAGTGGTG
S L F V T V P V S R P I L T L R V P R A Q A V V G D L 582
1761 AGCCTTTTTGTCACTGTTCCAGTGTCTCGCCCCATCCTCACCCTCAGGGTTCCCAGGGCCCAGGCTGTGGTGGGGGACCT
L E L H C E A P R G S P P I L Y W F Y H E D V T L G S609
1841 GCTGGAGCTTCACTGTGAGGCCCCGAGAGGCTCTCCCCCAATCCTGTACTGGTTTTATCATGAGGATGTCACCCTGGGGA
S S A P S G G E A S F N L S L T A E H S G N Y S C E 635
1921 GCAGCTCAGCCCCCTCTGGAGGAGAAGCTTCTTTCAACCTCTCTCTGACTGCAGAACATTCTGGAAACTACTCATGTGAG
A N N G L V A Q H S D T I S L S V I V P V S R P I L T 662
2001 GCCAACAATGGCCTAGTGGCCCAGCACAGTGACACAATATCACTCAGTGTTATAGTTCCAGTATCTCGTCCCATCCTCAC
F R A P R A Q A V V G D L L E L H C E A L R G S S P I689
2081 CTTCAGGGCTCCCAGGGCCCAGGCTGTGGTGGGGGACCTGCTGGAGCTTCACTGTGAGGCCCTGAGAGGCTCCTCCCCAA
L Y W F Y H E D V T L G K I S A P S G G G A S F N L 715
2161 TCCTGTACTGGTTTTATCATGAAGATGTCACCCTGGGTAAGATCTCAGCCCCCTCTGGAGGAGGGGCCTCCTTCAACCTC
S L T T E H S G I Y S C E A D N G L E A Q R S E M V T 742
2241 TCTCTGACTACAGAACATTCTGGAATCTACTCCTGTGAGGCAGACAATGGTCTGGAGGCCCAGCGCAGTGAGATGGTGAC
L K V A G E W A L P T S S T S E N * 759
2321 ACTGAAAGTTGCAGGTGAGTGGGCCCTGCCCACCAGCAGCACATCTGAGAACTGACTGTGCCTGTTCTCCCTGCAGCTGA
2401 AAATGGAGCCACAGAGCTCCTCAGGGCTGTTTGCTTGTGTGGCATCCCAGCACACTTCCTGCCTGCAGAACCTCCCTGTG
2481 AAAGTCTCGGATCCTTTGTGGTATGGTTCCAGGAATCTGATGTTTCCCAGCAGTCTTCTTGAAGATGATCAAAGCACCTC
2561 ACTAAAAATGCAAATAAGACTTTTTTAGAACATAAACTATATTCTGAACTGAAATTATTACATGAAAATGAAACCAAAGA
2641 ATTCTGAGCATATGTTTCTCTGCCGTAGAAAGGATTAAGCTGTTTCTTGTCCGGATTCTTCTCTCATTGACTTCTAAGAA
2721 GCCTCTACTCTTGAGTCTCTTTCATTACTGGGGATGTAAATGTTCCTTACATTTCCACATTAAAAATCCTATGTTAACGA
AAAAA

FIGURE 6b

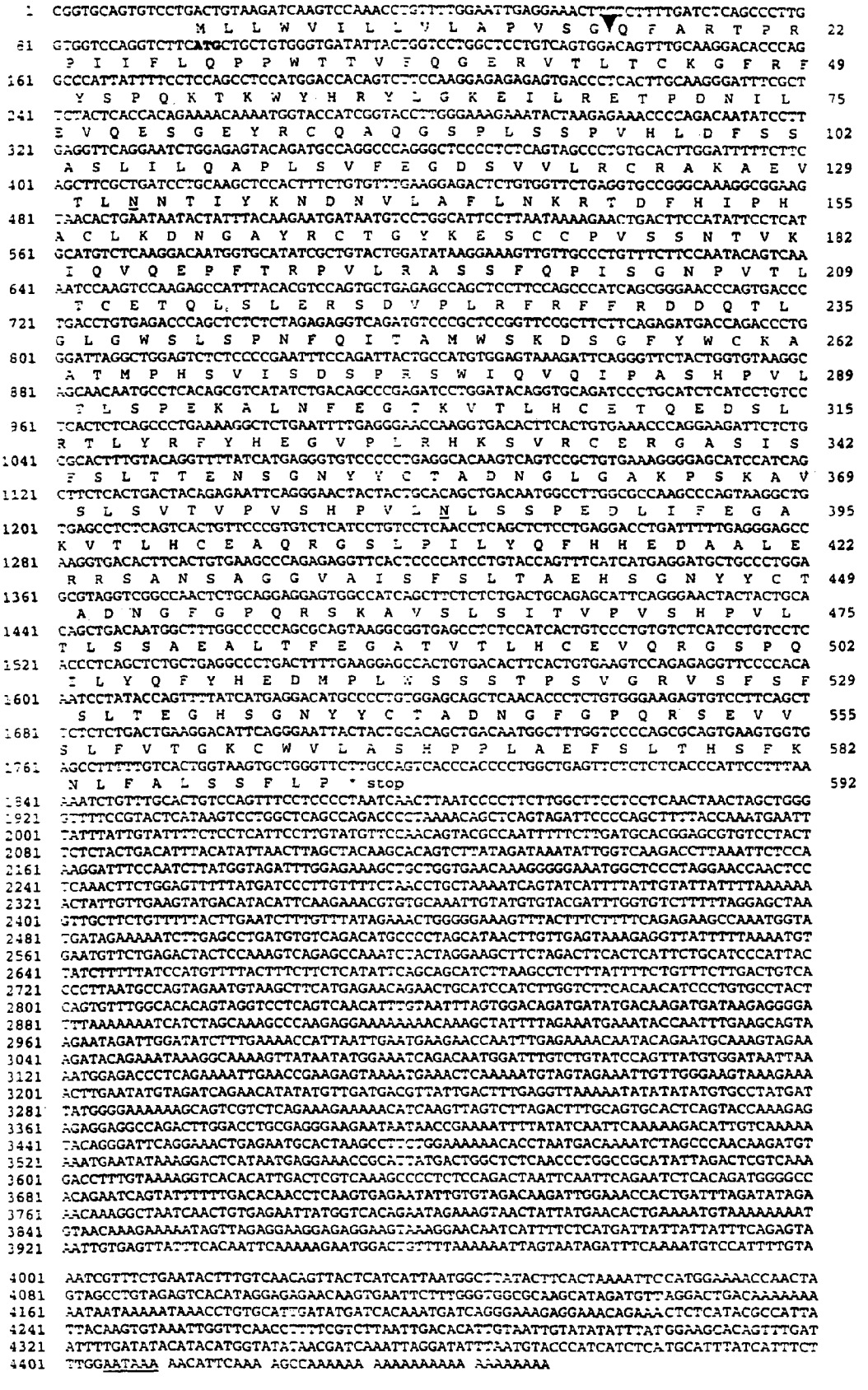


FIGURE 6c-1

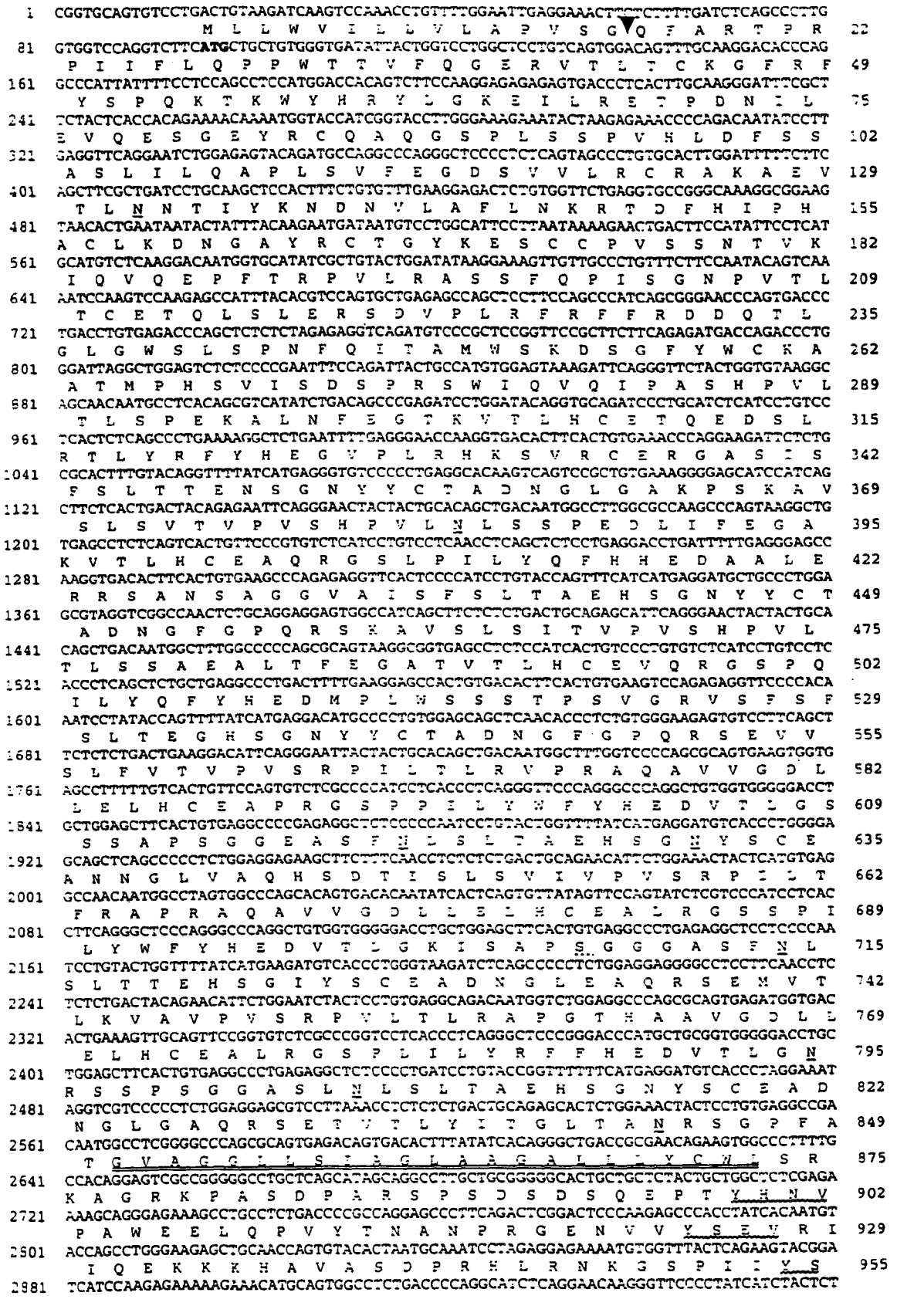
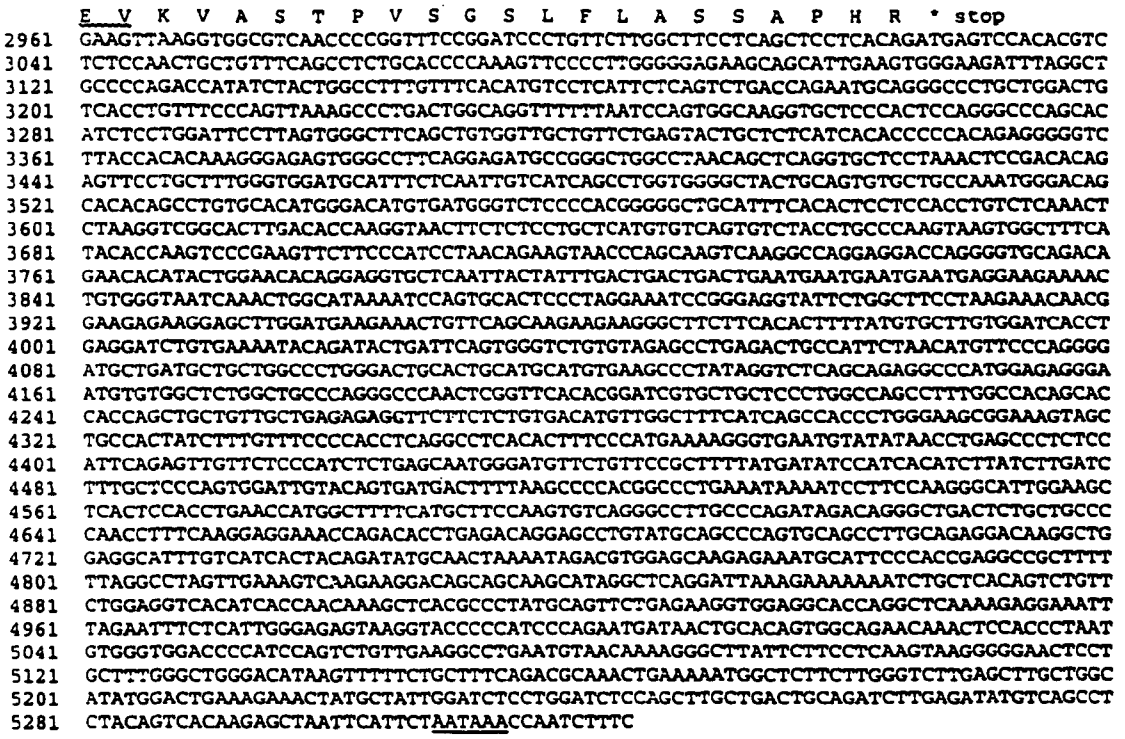


FIGURE 6c-2


E V K V A S T P V S G S L F L A S S A P H R * stop
977
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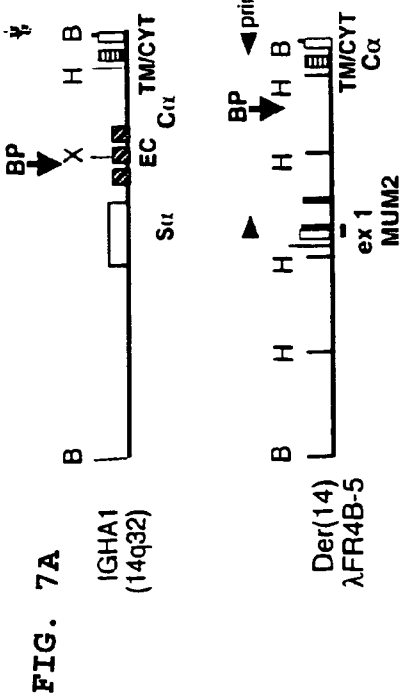
3041 TCTCCAACTGCTGTTTCAGCCTCTGCACCCCAAAGTTCCCCTTGGGGGAGAAGCAGCATTGAAGTGGGAAGATTTAGGCT
3121 GCCCCAGACCATATCTACTGGCCTTTGTTTCACATGTCCTCATTCTCAGTCTGACCAGAATGCAGGGCCCTGCTGGACTG
3201 TCACCTGTTTCCCAGTTAAAGCCCTGACTGGCAGGTTTTTTAATCCAGTGGCAAGGTGCTCCCACTCCAGGGCCCAGCAC
3281 ATCTCCTGGATTCCTTAGTGGGCTTCAGCTGTGGTTGCTGTTCTGAGTACTGCTCTCATCACACCCCCACAGAGGGGGTC
3361 TTACCACACAAAGGGAGAGTGGGCCTTCAGGAGATGCCGGGCTGGCCTAACAGCTCAGGTGCTCCTAAACTCCGACACAG
3441 AGTTCCTGCTTTGGGTGGATGCATTTCTCAATTGTCATCAGCCTGGTGGGGCTACTGCAGTGTGCTGCCAAATGGGACAG
3521 CACACAGCCTGTGCACATGGGACATGTGATGGGTCTCCCCACGGGGGCTGCATTTCACACTCCTCCACCTGTCTCAAACT
3601 CTAAGGTCGGCACTTGACACCAAGGTAACTTCTCTCCTGCTCATGTGTCAGTGTCTACCTGCCCAAGTAAGTGGCTTTCA
3681 TACACCAAGTCCCGAAGTTCTTCCCATCCTAACAGAAGTAACCCAGCAAGTCAAGGCCAGGAGGACCAGGGGTGCAGACA
3761 GAACACATACTGGAACACAGGAGGTGCTCAATTACTATTTGACTGACTGACTGAATGAATGAATGAATGAGGAAGAAAAC
3841 TGTGGGTAATCAAACTGGCATAAAATCCAGTGCACTCCCTAGGAAATCCGGGAGGTATTCTGGCTTCCTAAGAAACAACG
3921 GAAGAGAAGGAGCTTGGATGAAGAAACTGTTCAGCAAGAAGAAGGGCTTCTTCACACTTTTATGTGCTTGTGGATCACCT
4001 GAGGATCTGTGAAAATACAGATACTGATTCAGTGGGTCTGTGTAGAGCCTGAGACTGCCATTCTAACATGTTCCCAGGGG
4081 ATGCTGATGCTGCTGGCCCTGGGACTGCACTGCATGCATGTGAAGCCCTATAGGTCTCAGCAGAGGCCCATGGAGAGGGA
4161 ATGTGTGGCTCTGGCTGCCCAGGGCCCAACTCGGTTCACACGGATCGTGCTGCTCCCTGGCCAGCCTTTGGCCACAGCAC
4241 CACCAGCTGCTGTTGCTGAGAGAGGTTCTTCTCTGTGACATGTTGGCTTTCATCAGCCACCCTGGGAAGCGGAAAGTAGC
4321 TGCCACTATCTTTGTTTCCCCACCTCAGGCCTCACACTTTCCCATGAAAAGGGTGAATGTATATAACCTGAGCCCTCTCC
4401 ATTCAGAGTTGTTCTCCCATCTCTGAGCAATGGGATGTTCTGTTCCGCTTTTATGATATCCATCACATCTTATCTTGATC
4481 TTTGCTCCCAGTGGATTGTACAGTGATGACTTTTAAGCCCCACGGCCCTGAAATAAAATCCTTCCAAGGGCATTGGAAGC
4561 TCACTCCACCTGAACCATGGCTTTTCATGCTTCCAAGTGTCAGGGCCTTGCCCAGATAGACAGGGCTGACTCTGCTGCCC
4641 CAACCTTTCAAGGAGGAAACCAGACACCTGAGACAGGAGCCTGTATGCAGCCCAGTGCAGCCTTGCAGAGGACAAGGCTG
4721 GAGGCATTTGTCATCACTACAGATATGCAACTAAAATAGACGTGGAGCAAGAGAAATGCATTCCCACCGAGGCCGCTTTT
4801 TTAGGCCTAGTTGAAAGTCAAGAAGGACAGCAGCAAGCATAGGCTCAGGATTAAAGAAAAAAATCTGCTCACAGTCTGTT
4881 CTGGAGGTCACATCACCAACAAAGCTCACGCCCTATGCAGTTCTGAGAAGGTGGAGGCACCAGGCTCAAAAGAGGAAATT
4961 TAGAATTTCTCATTGGGAGAGTAAGGTACCCCCATCCCAGAATGATAACTGCACAGTGGCAGAACAAACTCCACCCTAAT
5041 GTGGGTGGACCCCATCCAGTCTGTTGAAGGCCTGAATGTAACAAAAGGGCTTATTCTTCCTCAAGTAAGGGGGAACTCCT
5121 GCTTTGGGCTGGGACATAAGTTTTTCTGCTTTCAGACGCAAACTGAAAAATGGCTCTTCTTGGGTCTTGAGCTTGCTGGC
5201 ATATGGACTGAAAGAAACTATGCTATTGGATCTCCTGGATCTCCAGCTTGCTGACTGCAGATCTTGAGATATGTCAGCCT
5281 CTACAGTCACAAGAGCTAATTCATTCTAATAAACCAATCTTTC

FIGURE 7



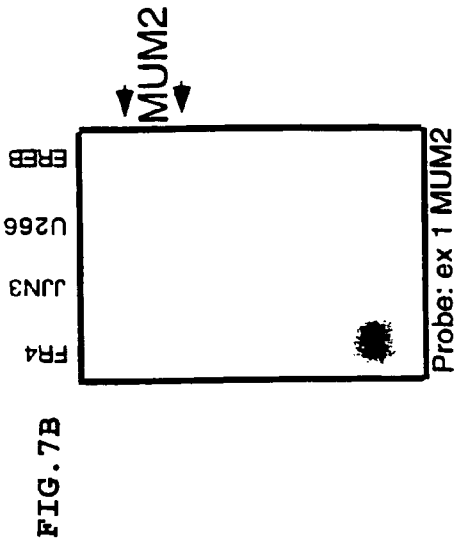


FIG. 7C

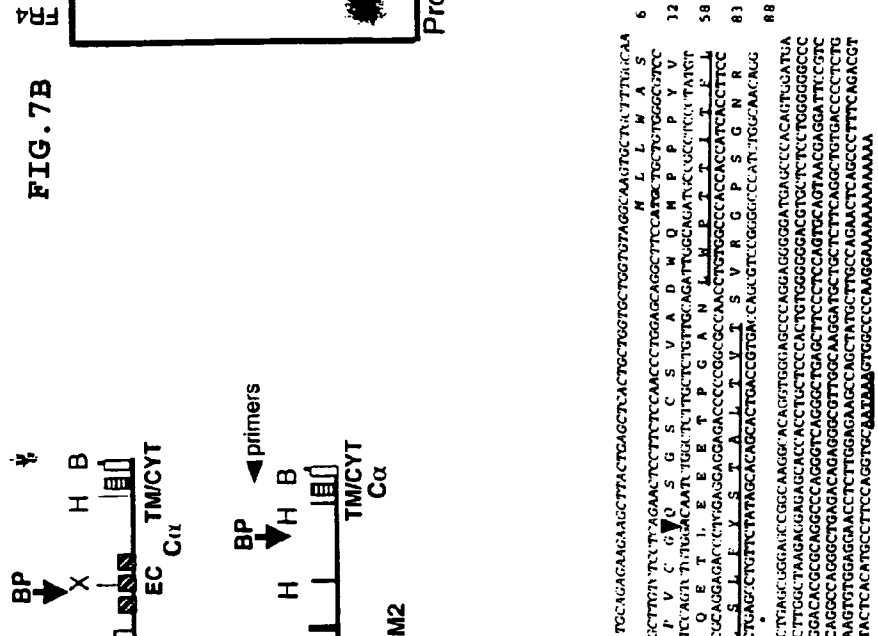


FIG.8B

FIGURE 8

```
Chr  14  TCCCACTGACGCATGCAGGAAGGGGCACCTCCCCTTAACCACACTGCTCTGTACGGGGCACGTGGGCACAGGTGCACACTCACACTCACA
                                                 ||||||||||||||||||||||||||||||||||||||||||||||||||
Der (14) GGCCTGACAGCAACTTTTCTTCTACTAGTTCATCTTAA-CACACTGCTCTGTACGGGGCACGTGGGCACAGGTGCACACTCACACTCACA
         ||||||||||||||||||||||||||||||||||||
Chr   1  GGCCTGACAGCAACTTTTCTTCTACTAGTTCATCTTAACTTTATCCTGGTAACTGGCGAGACAACCTGTCTTAAGTAACTGAAGGGAAA


Chr   1  GGCCTGACAGCAACTTTTCTTCTACTAGTTCATCTTAACTTTATCCTGGTAACTGGCGAGACAACCTGTCTTAAGTAACTGAAGGGAAA
                                        |||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Der  (1)          TCCCACTGACGCA----GGAAGGATCTTAAGTTTATCCTGGTAACTGGCGAGACAACCTGTCTTAAGTAACTGAAGGGAAA
                  |||||||||||||    ||||||
Chr  14           TCCCACTGACGCATGCAGGAAGGGGCACCTCCCCTTAACCACACTGCTCTGTACGGGGCACGTGGGCACAGGTGCACACTCACACTCACA
```

8c

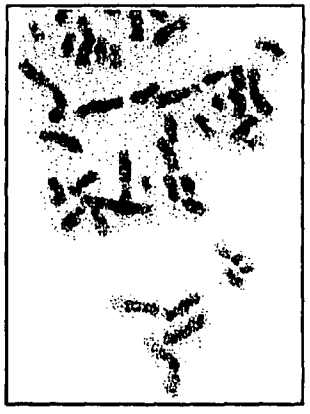


FIGURE 8A

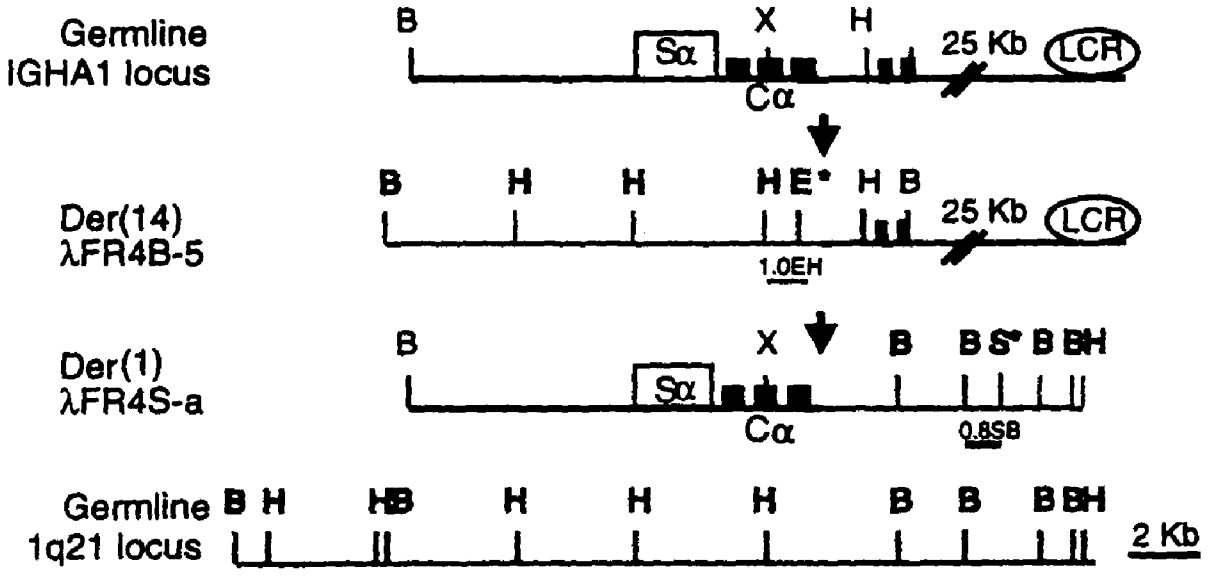

Germline
IGHA1 locus
B
X
H
Sα
Cα
25 Kb
LCR
Der(14)
λFR4B-5
B H H HE* H B
1.0EH
Der(1)
λFR4S-a
B X B BS* B BH
0.8SB
Germline
1q21 locus
B H HB H H H B B BBH
2 Kb

FIGURE 9

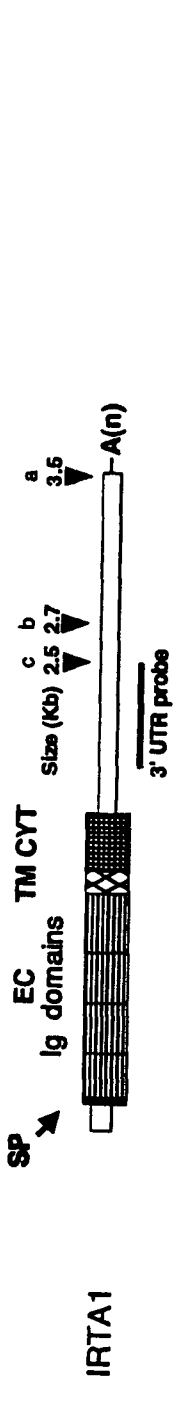


FIG. 9A

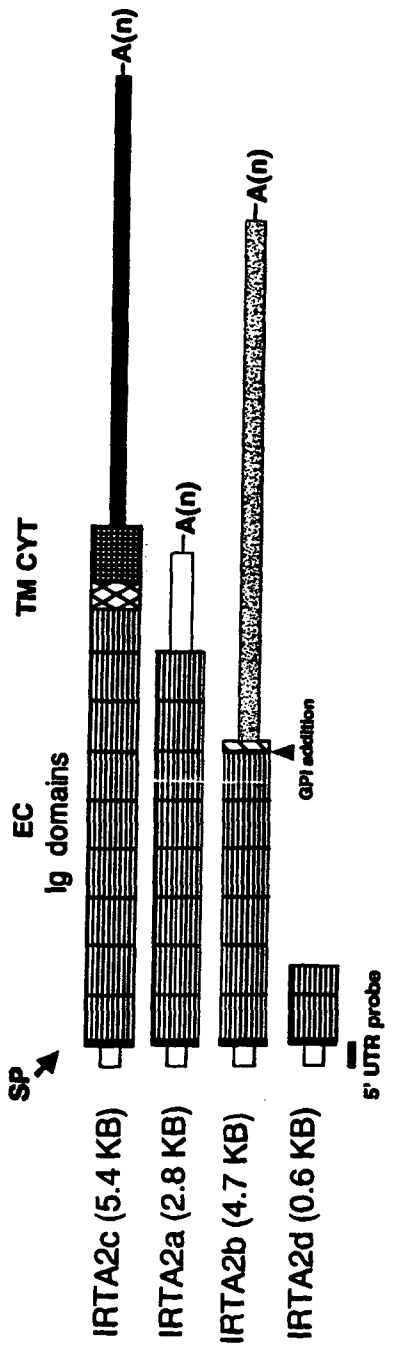


FIG. 9B

FIGURE 10

FIG.10A

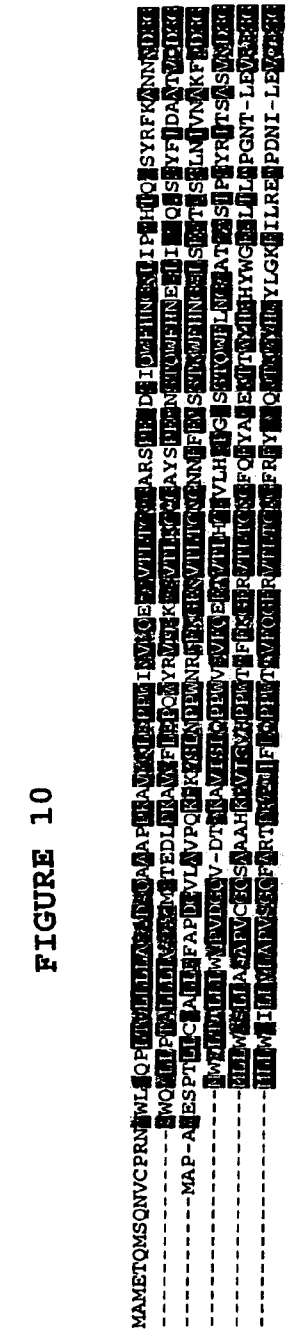
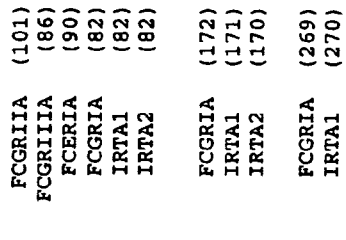


FIG.10B



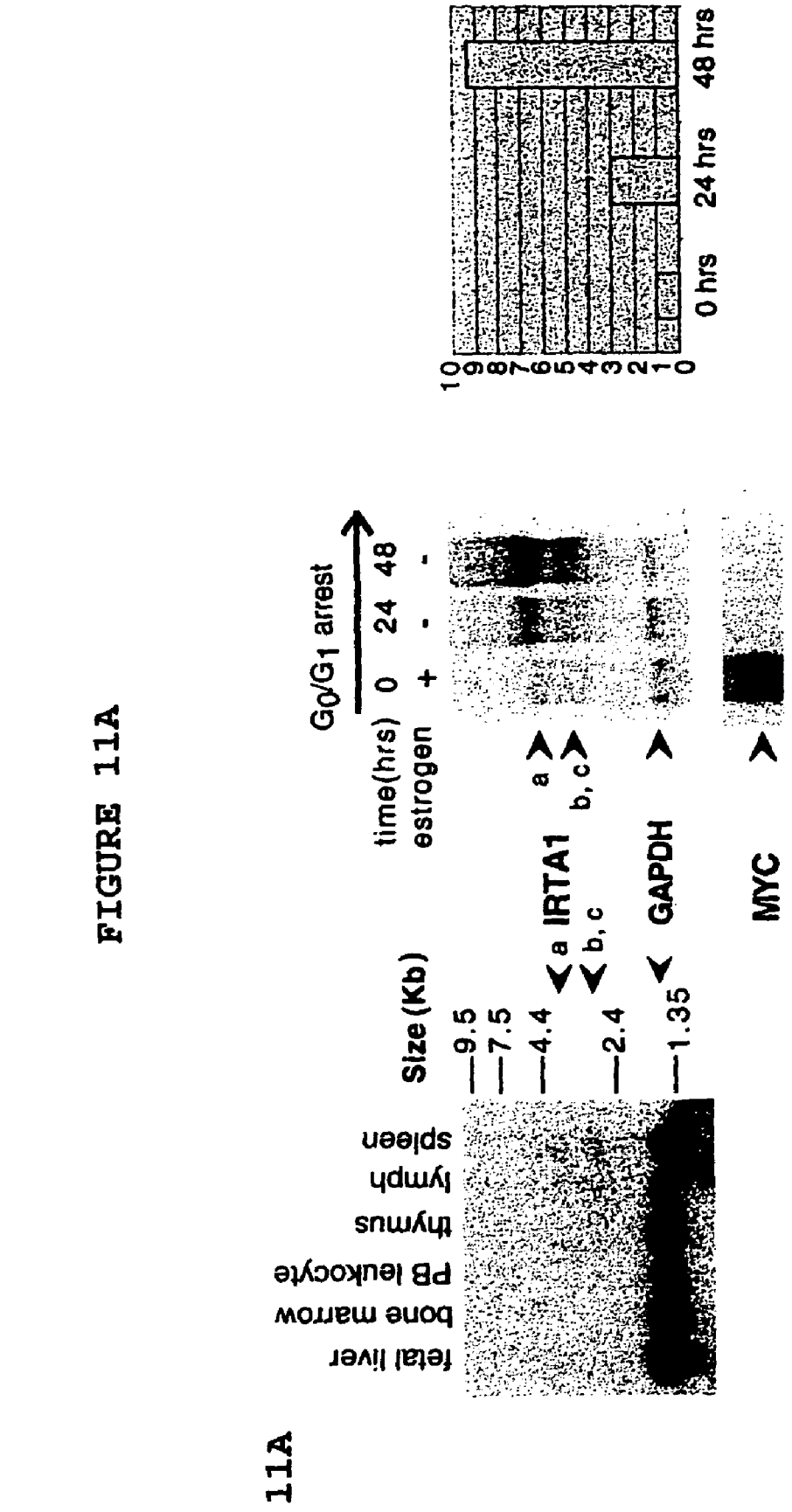


FIGURE 11A

11A

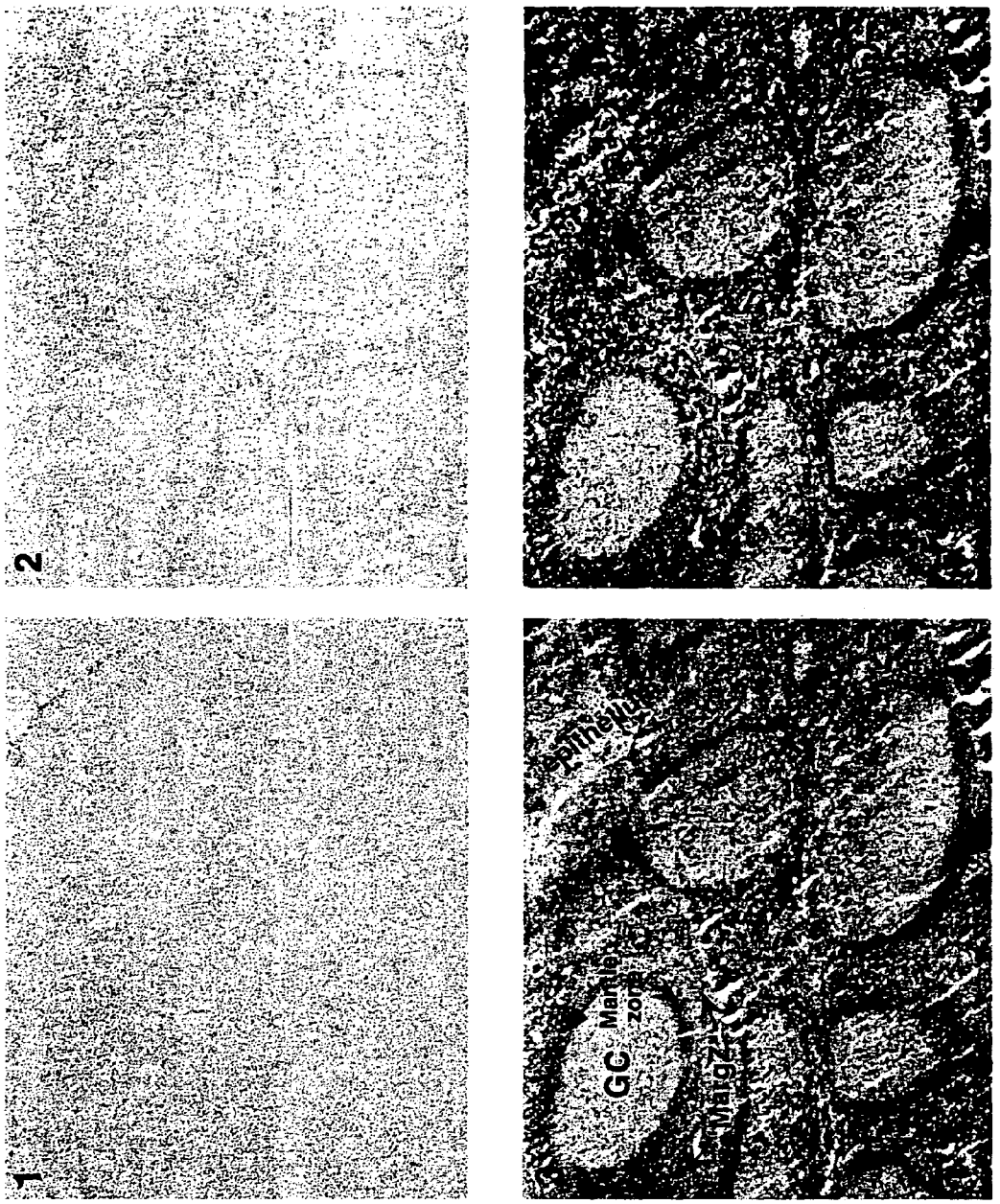
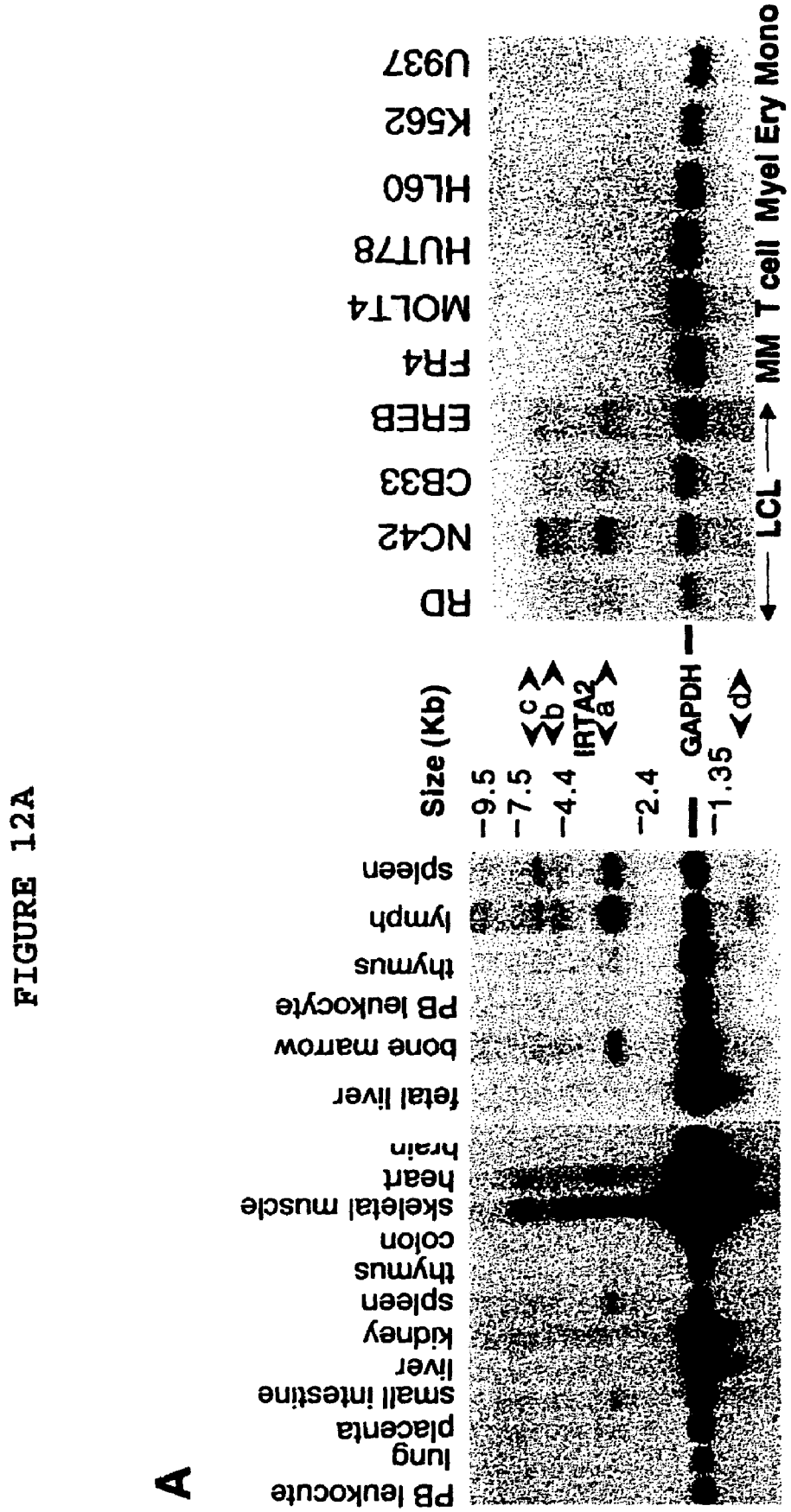


FIGURE 11B1-B4

FIGURE 12A


A
PB leukocyte
lung
placenta
small intestine
liver
kidney
spleen
thymus
colon
skeletal muscle
heart
brain
fetal liver
bone marrow
PB leukocyte
thymus
lymph
spleen
Size (Kb)
9.5
7.5
4.4
2.4
1.35
c
b
IRTA2
a
GAPDH
d
RD
NC42
CB33
EREB
FR4
MOLT4
HUT78
HL60
K562
U937
LCL
MM T cell Myel Ery Mono

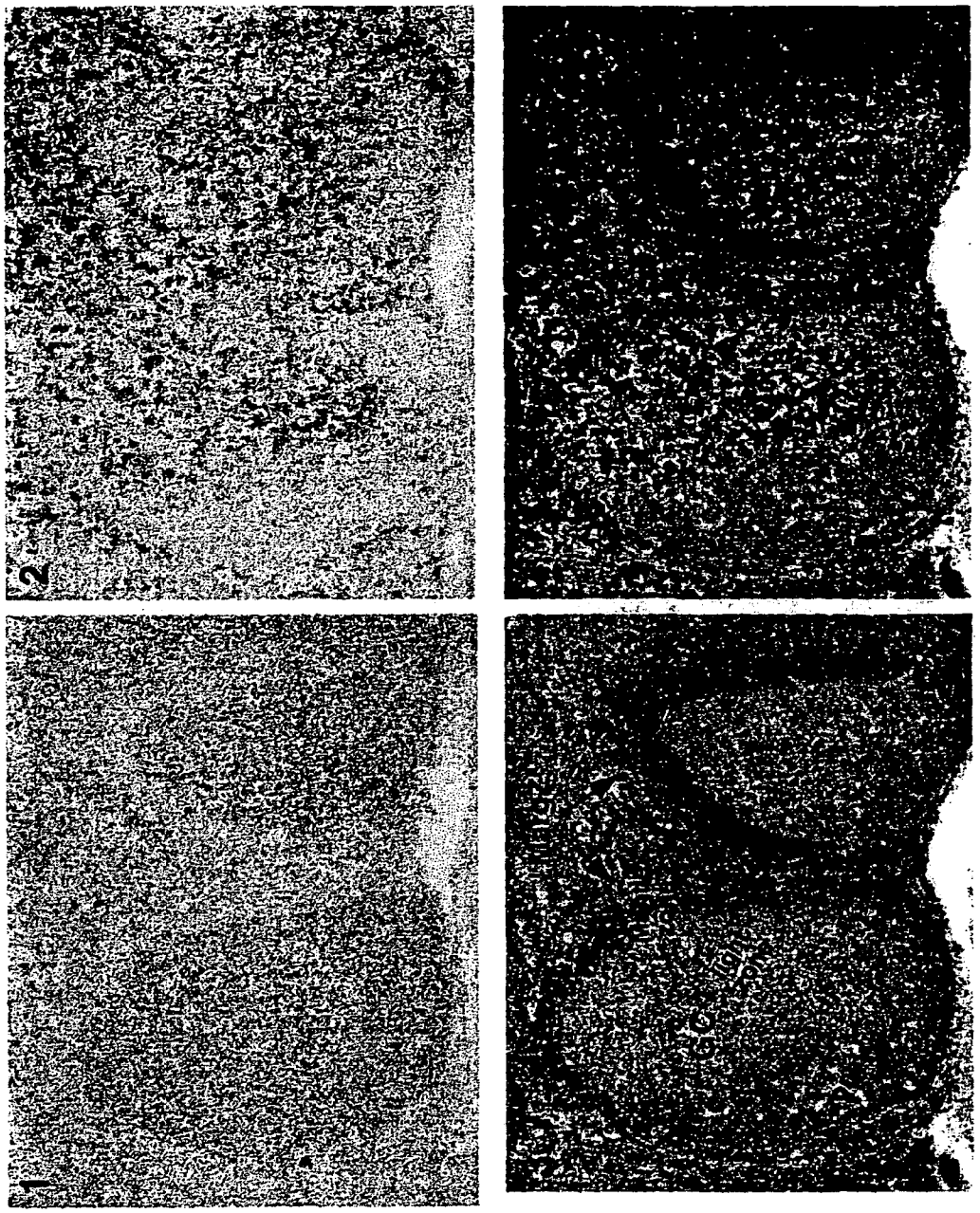
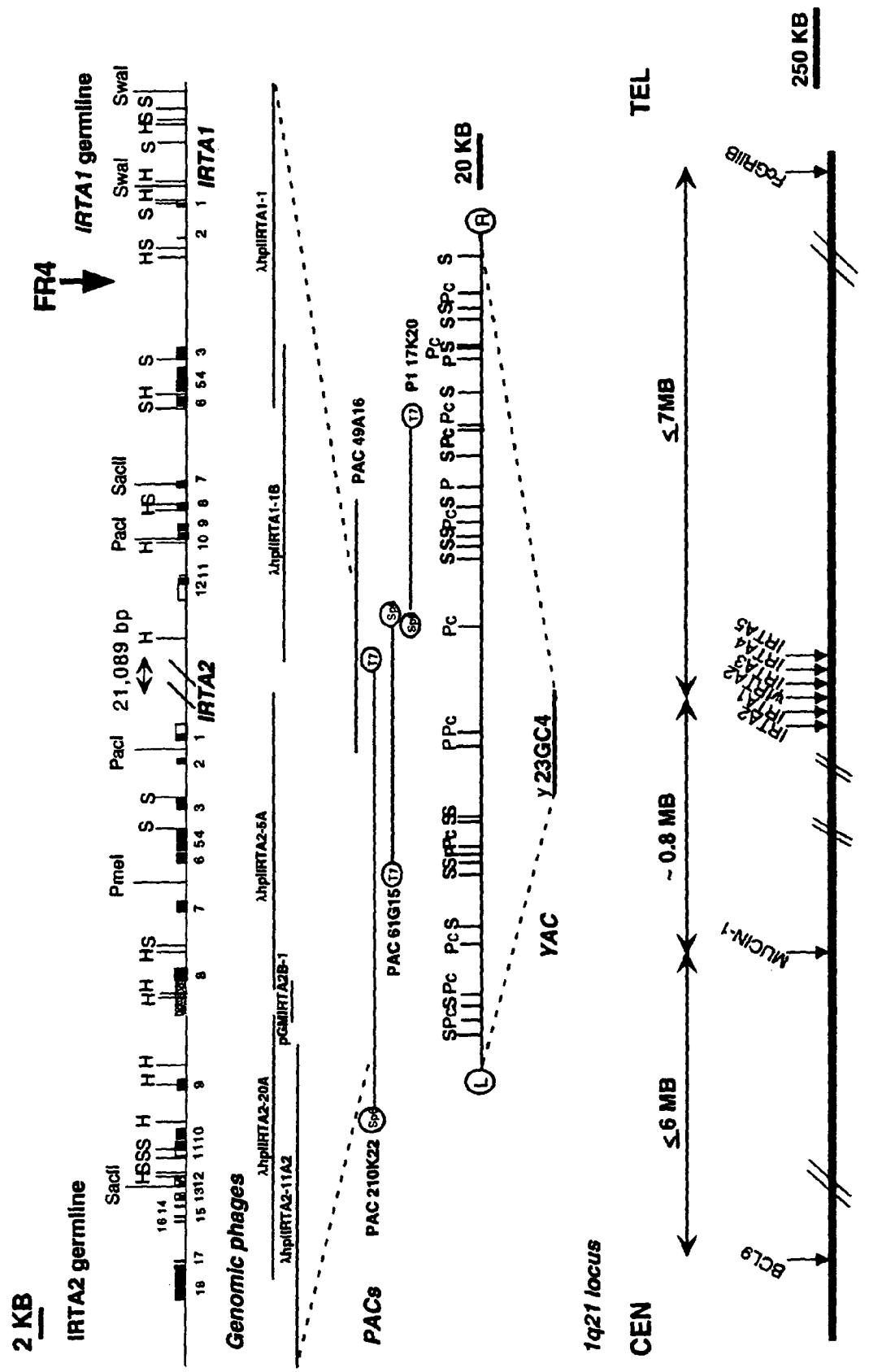


FIGURE 12B1-B4

B

FIGURE 13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IRTA2 germline
IRTA1 germline
FR4
IRTA2
IRTA1
21,089 bp
Genomic phages
PACs
YAC
20 KB
250 KB
1q21 locus
CEN
TEL
≤6 MB
~0.8 MB
≤7MB
MUCIN-1
BCL9
FCGR1B
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PAC 49A16
P1 17K20
y23GC4

FIGURE 14

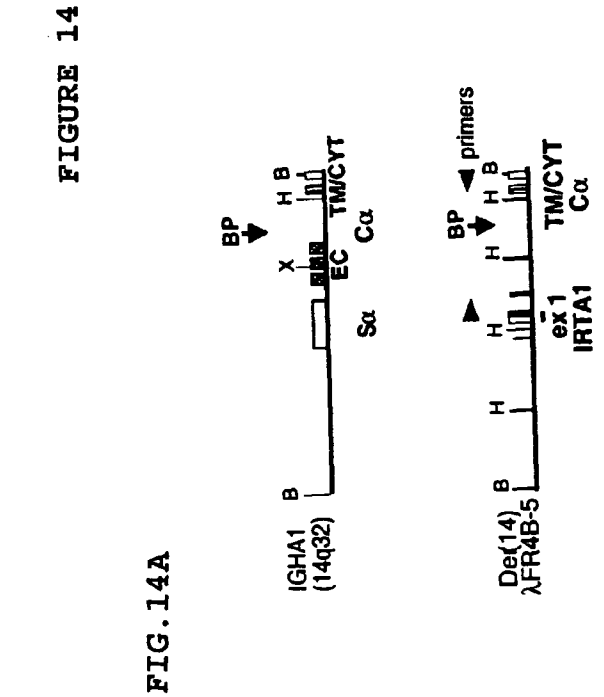


FIG.14A

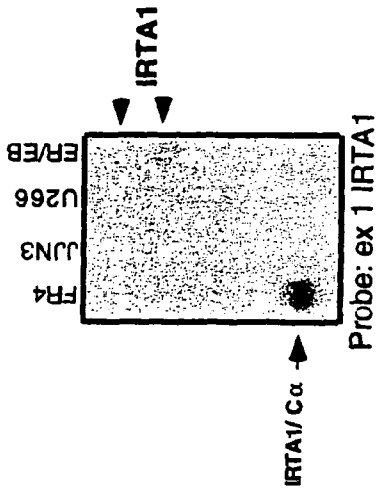


FIG.14B

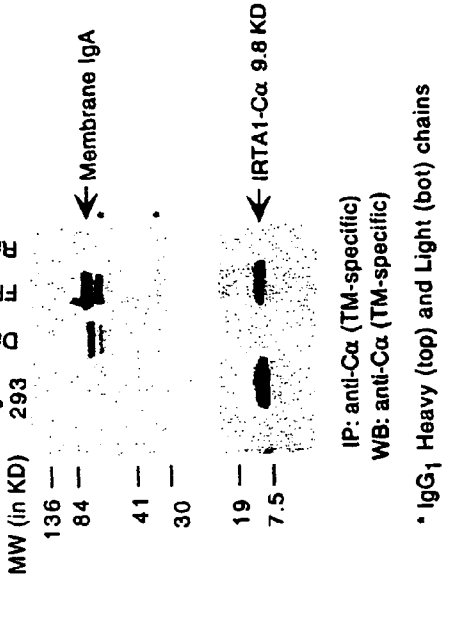


FIG.14D

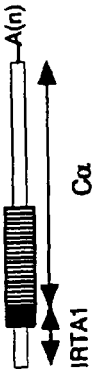
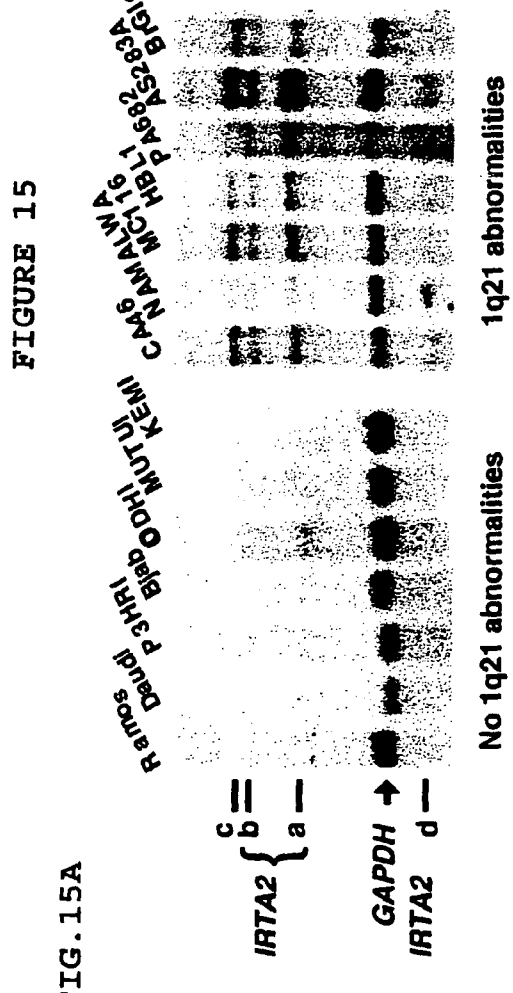


FIG.14C

FIGURE 15

FIG.15A



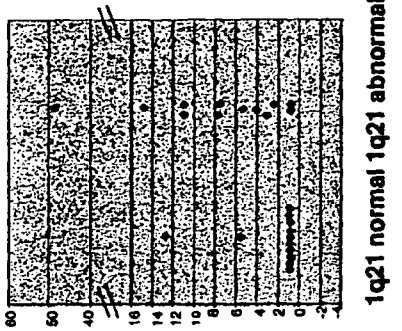


FIG.15B

Cell line	IRTA2
Burkitt Lymphoma	
Normal 1q21	2/12
Abnormal 1q21	10/12
Multiple Myeloma	
Normal 1q21	0/7
Abnormal 1q21	1/3

Summary of *IRTA2* expression

FIGURE 16

IRTA1 expression in normal lymphoid tissue

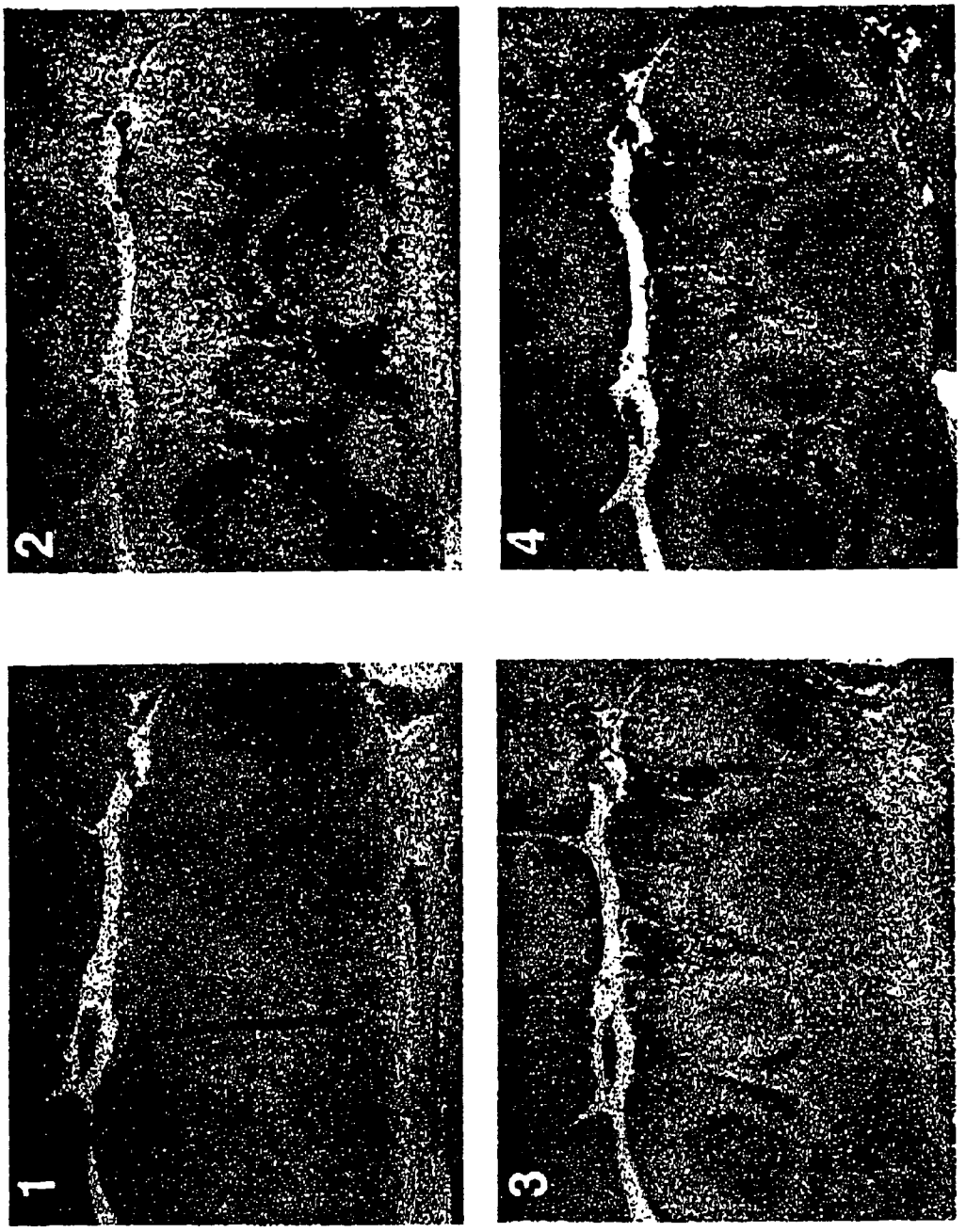


FIGURE 17

IRTA1 expression in a stomach Mucosa-Associated-Lymphoid Tissue B cell lymphoma

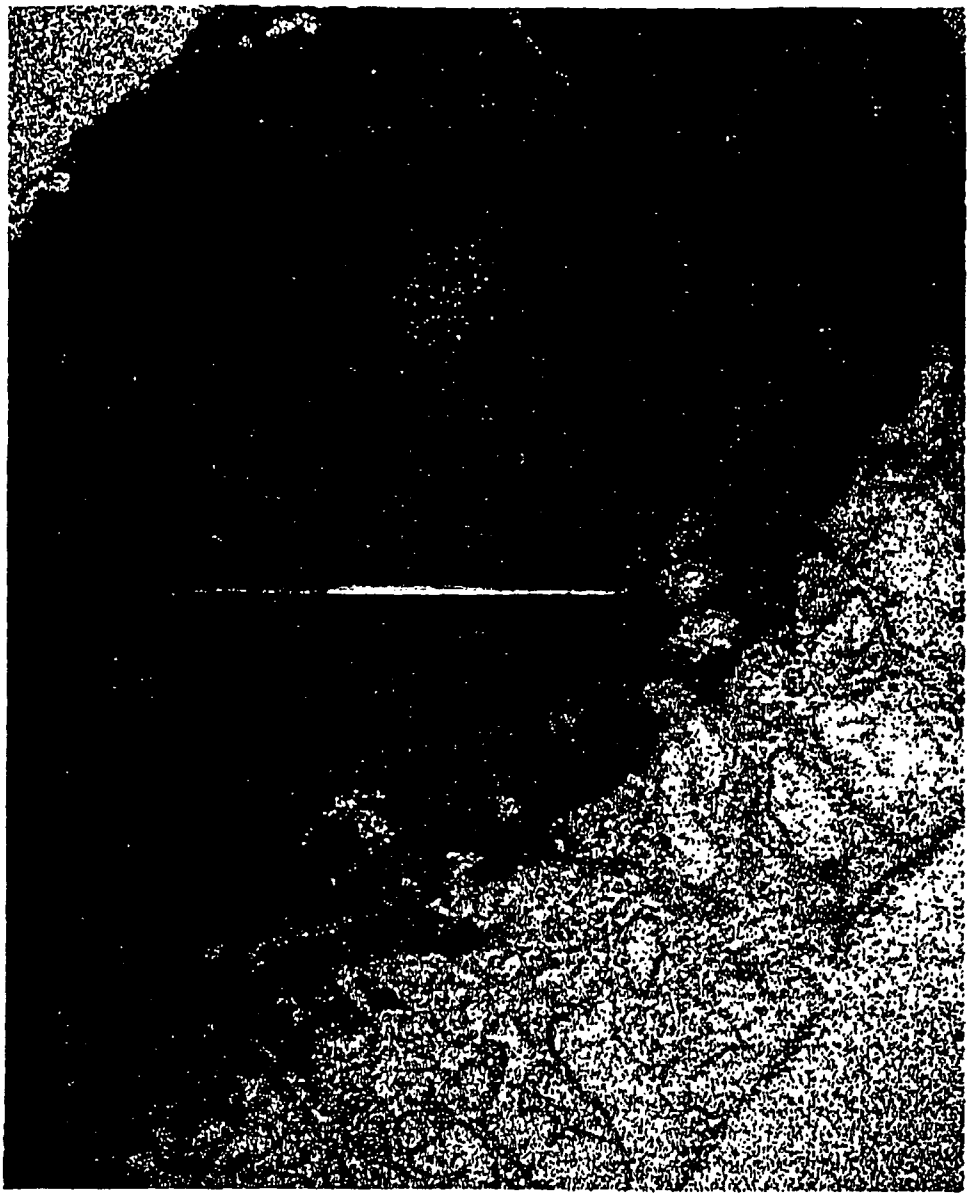
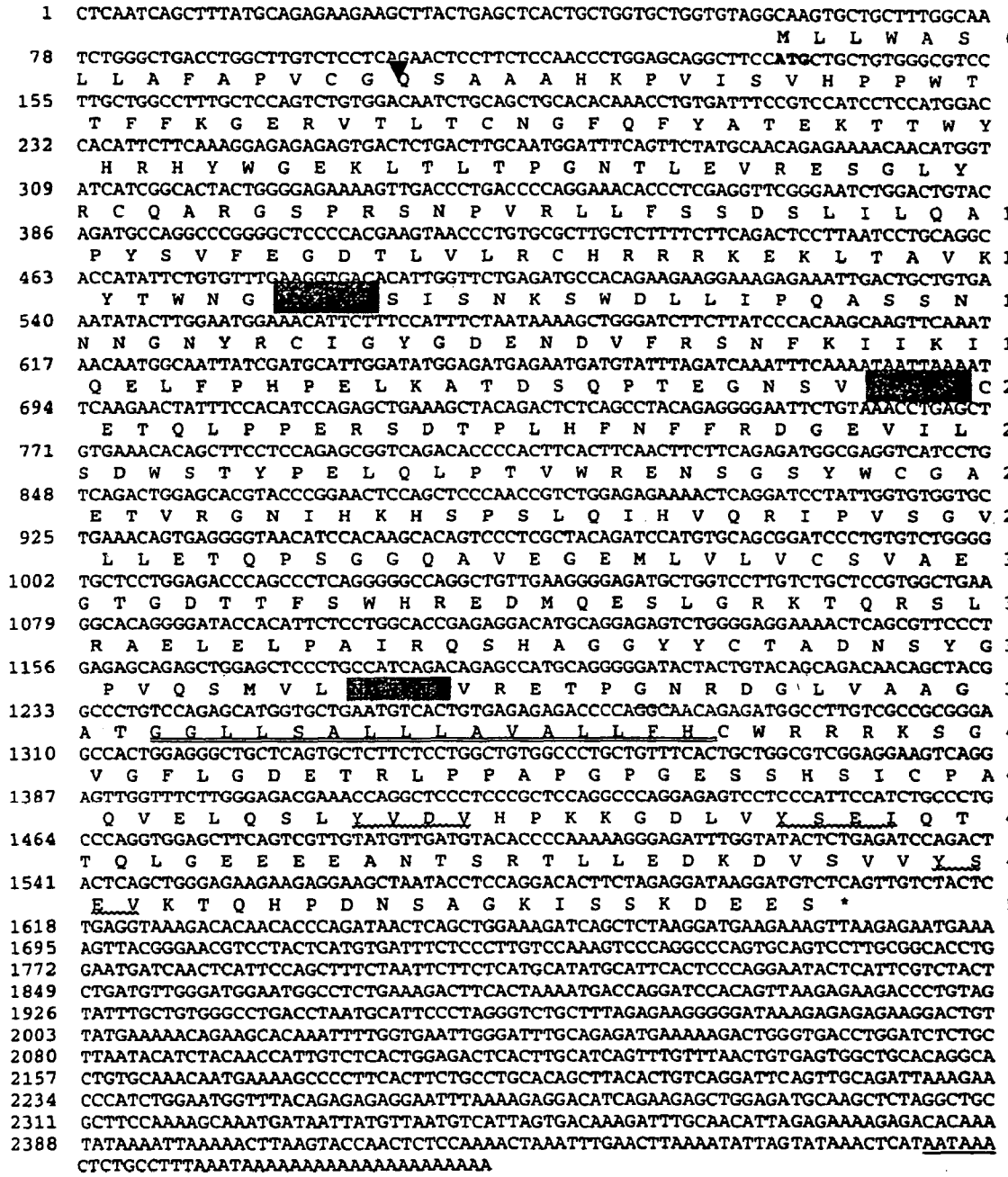


FIGURE 18A



IRTA1 cDNA and protein sequence

FIGURE 18B-1

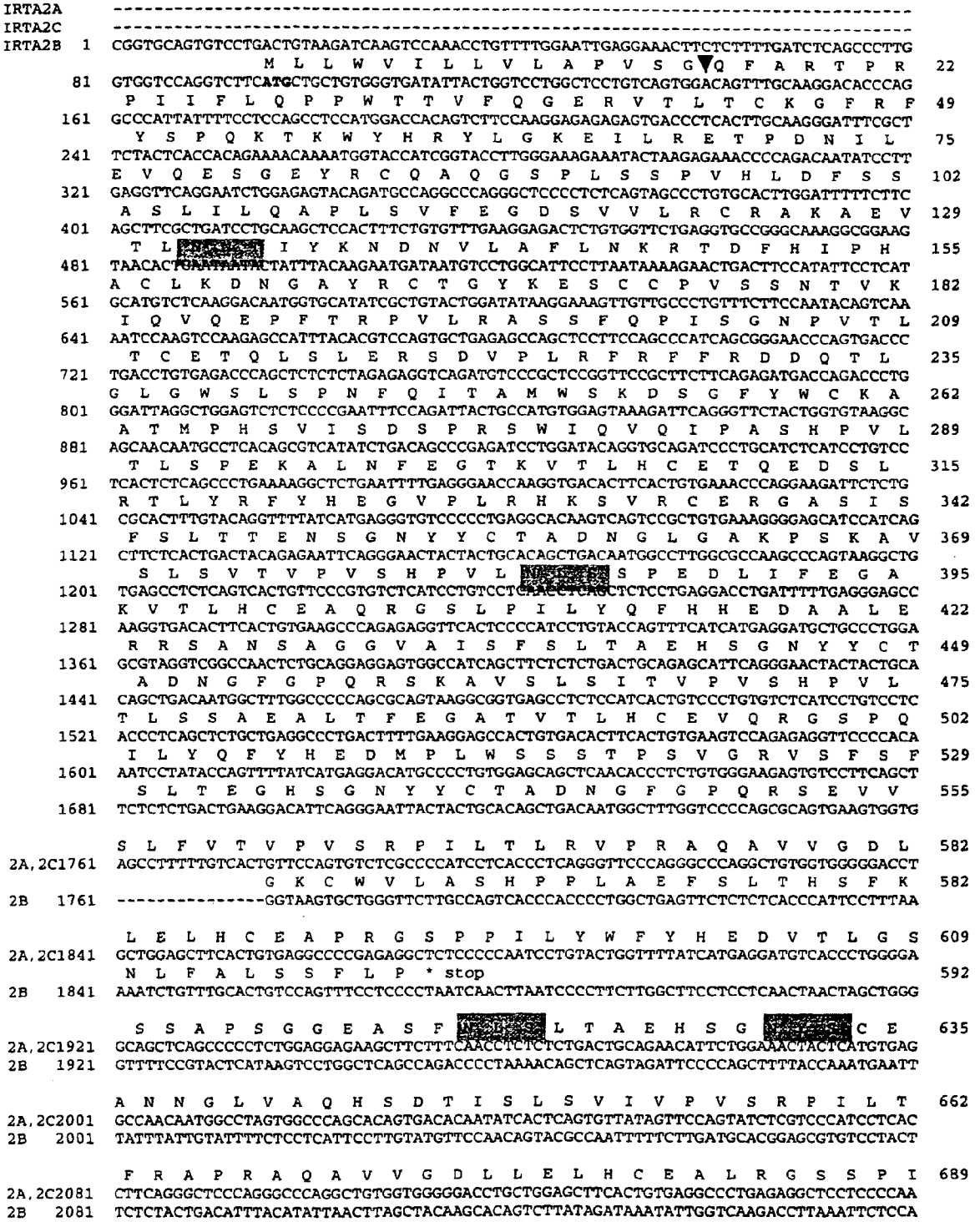

IRTA2A
IRTA2C
IRTA2B 1
M L L W V I L L V L A P V S G Q F A R T P R 22
81 GTGGTCCAGGTCTTCATGCTGCTGTGGGTGATATTACTGGTCCTGGCTCCTGTCAGTGGACAGTTTGCAAGGACACCCAG
P I I F L Q P P W T T V F Q G E R V T L T C K G F R F 49
161 GCCCATTATTTTCCTCCAGCCTCCATGGACCACAGTCTTCCAAGGAGAGAGAGTGACCCTCACTTGCAAGGGATTTCGCT
Y S P Q K T K W Y H R Y L G K E I L R E T P D N I L 75
241 TCTACTCACCACAGAAAACAAAATGGTACCATCGGTACCTTGGGAAAGAAATACTAAGAGAAACCCCAGACAATATCCTT
E V Q E S G E Y R C Q A Q G S P L S S P V H L D F S S 102
321 GAGGTTCAGGAATCTGGAGAGTACAGATGCCAGGCCCAGGGCTCCCCTCTCAGTAGCCCTGTGCACTTGGATTTTTCTTC
A S L I L Q A P L S V F E G D S V V L R C R A K A E V 129
401 AGCTTCGCTGATCCTGCAAGCTCCACTTTCTGTGTTTGAAGGAGACTCTGTGGTTCTGAGGTGCCGGGCAAAGGCGGAAG
T L [redacted] I Y K N D N V L A F L N K R T D F H I P H 155
481 TAACAC[redacted]TACTATTTACAAGAATGATAATGTCCTGGCATTCCTTAATAAAAGAACTGACTTCCATATTCCTCAT
A C L K D N G A Y R C T G Y K E S C C P V S S N T V K 182
561 GCATGTCTCAAGGACAATGGTGCATATCGCTGTACTGGATATAAGGAAAGTTGTTGCCCTGTTTCTTCCAATACAGTCAA
I Q V Q E P F T R P V L R A S S F Q P I S G N P V T L 209
641 AATCCAAGTCCAAGAGCCATTTACACGTCCAGTGCTGAGAGCCAGCTCCTTCCAGCCCATCAGCGGGAACCCAGTGACCC
T C E T Q L S L E R S D V P L R F R F F R D D Q T L 235
721 TGACCTGTGAGACCCAGCTCTCTCTAGAGAGGTCAGATGTCCCGCTCCGGTTCCGCTTCTTCAGAGATGACCAGACCCTG
G L G W S L S P N F Q I T A M W S K D S G F Y W C K A 262
801 GGATTAGGCTGGAGTCTCTCCCCGAATTTCCAGATTACTGCCATGTGGAGTAAAGATTCAGGGTTCTACTGGTGTAAGGC
A T M P H S V I S D S P R S W I Q V Q I P A S H P V L 289
881 AGCAACAATGCCTCACAGCGTCATATCTGACAGCCCGAGATCCTGGATACAGGTGCAGATCCCTGCATCTCATCCTGTCC
T L S P E K A L N F E G T K V T L H C E T Q E D S L 315
961 TCACTCTCAGCCCTGAAAAGGCTCTGAATTTTGAGGGAACCAAGGTGACACTTCACTGTGAAACCCAGGAAGATTCTCTG
R T L Y R F Y H E G V P L R H K S V R C E R G A S I S 342
1041 CGCACTTTGTACAGGTTTTATCATGAGGGTGTCCCCCTGAGGCACAAGTCAGTCCGCTGTGAAAGGGGAGCATCCATCAG
F S L T T E N S G N Y Y C T A D N G L G A K P S K A V 369
1121 CTTCTCACTGACTACAGAGAATTCAGGGAACTACTACTGCACAGCTGACAATGGCCTTGGCGCCAAGCCCAGTAAGGCTG
S L S V T V P V S H P V L [redacted] S P E D L I F E G A 395
1201 TGAGCCTCTCAGTCACTGTTCCCGTGTCTCATCCTGTCCT[redacted]CTCCTGAGGACCTGATTTTTGAGGGAGCC
K V T L H C E A Q R G S L P I L Y Q F H H E D A A L E 422
1281 AAGGTGACACTTCACTGTGAAGCCCAGAGAGGTTCACTCCCCATCCTGTACCAGTTTCATCATGAGGATGCTGCCCTGGA
R R S A N S A G G V A I S F S L T A E H S G N Y Y C T 449
1361 GCGTAGGTCGGCCAACTCTGCAGGAGGAGTGGCCATCAGCTTCTCTCTGACTGCAGAGCATTCAGGGAACTACTACTGCA
A D N G F G P Q R S K A V S L S I T V P V S H P V L 475
1441 CAGCTGACAATGGCTTTGGCCCCCAGCGCAGTAAGGCGGTGAGCCTCTCCATCACTGTCCCTGTGTCTCATCCTGTCCTC
T L S S A E A L T F E G A T V T L H C E V Q R G S P Q 502
1521 ACCCTCAGCTCTGCTGAGGCCCTGACTTTTGAAGGAGCCACTGTGACACTTCACTGTGAAGTCCAGAGAGGTTCCCCACA
I L Y Q F Y H E D M P L W S S S T P S V G R V S F S F 529
1601 AATCCTATACCAGTTTTATCATGAGGACATGCCCCTGTGGAGCAGCTCAACACCCTCTGTGGGAAGAGTGTCCTTCAGCT
S L T E G H S G N Y Y C T A D N G F G P Q R S E V V 555
1681 TCTCTCTGACTGAAGGACATTCAGGGAATTACTACTGCACAGCTGACAATGGCTTTGGTCCCCAGCGCAGTGAAGTGGTG
S L F V T V P V S R P I L T L R V P R A Q A V V G D L 582
2A,2C1761 AGCCTTTTTGTCACTGTTCCAGTGTCTCGCCCCATCCTCACCCTCAGGGTTCCCAGGGCCCAGGCTGTGGTGGGGGACCT
G K C W V L A S H P P L A E F S L T H S F K 582
2B 1761 ----------GGTAAGTGCTGGGTTCTTGCCAGTCACCCACCCCTGGCTGAGTTCTCTCTCACCCATTCCTTTAA
L E L H C E A P R G S P P I L Y W F Y H E D V T L G S 609
2A,2C1841 GCTGGAGCTTCACTGTGAGGCCCCGAGAGGCTCTCCCCCAATCCTGTACTGGTTTTATCATGAGGATGTCACCCTGGGGA
N L F A L S S F L P * stop 592
2B 1841 AAATCTGTTTGCACTGTCCAGTTTCCTCCCCTAATCAACTTAATCCCCTTCTTGGCTTCCTCCTCAACTAACTAGCTGGG
S S A P S G G E A S F [redacted] L T A E H S G [redacted] C E 635
2A,2C1921 GCAGCTCAGCCCCCTCTGGAGGAGAAGCTTCTTTCAACCTCTCTCTGACTGCAGAACATTCTGGAAACTACTCATGTGAG
2B 1921 GTTTTCCGTACTCATAAGTCCTGGCTCAGCCAGACCCCTAAAACAGCTCAGTAGATTCCCCAGCTTTTACCAAATGAATT
A N N G L V A Q H S D T I S L S V I V P V S R P I L T 662
2A,2C2001 GCCAACAATGGCCTAGTGGCCCAGCACAGTGACACAATATCACTCAGTGTTATAGTTCCAGTATCTCGTCCCATCCTCAC
2B 2001 TATTTATTGTATTTTCTCCTCATTCCTTGTATGTTCCAACAGTACGCCAATTTTTCTTGATGCACGGAGCGTGTCCTACT
F R A P R A Q A V V G D L L E L H C E A L R G S S P I 689
2A,2C2081 CTTCAGGGCTCCCAGGGCCCAGGCTGTGGTGGGGGACCTGCTGGAGCTTCACTGTGAGGCCCTGAGAGGCTCCTCCCCAA
2B 2081 TCTCTACTGACATTTACATATTAACTTAGCTACAAGCACAGTCTTATAGATAAATATTGGTCAAGACCTTAAATTCTCCA

FIGURE 18B-2

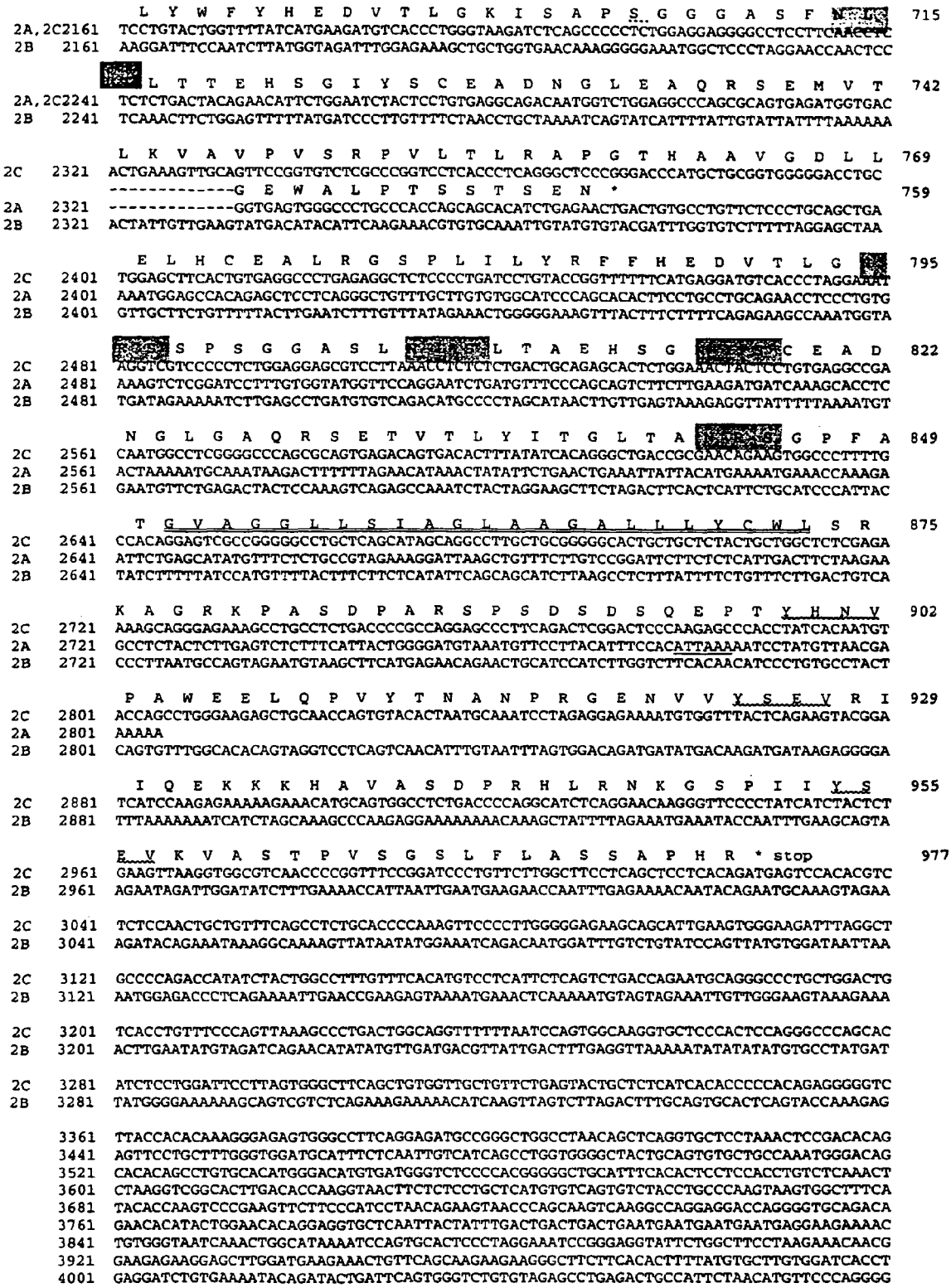


FIGURE 18B-3

```
4081  ATGCTGATGCTGCTGGCCCTGGGACTGCACTGCATGCATGTGAAGCCCTATAGGTCTCAGCAGAGGCCCATGGAGAGGGA
4161  ATGTGTGGCTCTGGCTGCCCAGGGCCCAACTCGGTTCACACGGATCGTGCTGCTCCCTGGCCAGCCTTTGGCCACAGCAC
4241  CACCAGCTGCTGTTGCTGAGAGAGCTTCTTCTCTGTGACATGTTGGCTTTCATCAGCCACCCTGGGAAGCGGAAAGTAGC
4321  TGCCACTATCTTTGTTTCCCCACCTCAGGCCTCACACTTTCCCATGAAAAGGGTGAATGTATATAACCTGAGCCCTCTCC
4401  ATTCAGAGTTGTTCTCCCATCTCTGAGCAATGGGATGTTCTGTTCCGCTTTTATGATATCCATCACATCTTATCTTGATC
4481  TTTGCTCCCAGTGGATTGTACAGTGATGACTTTTAAGCCCCACGGCCCTGAAATAAAATCCTTCCAAGGGCATTGGAAGC
4561  TCACTCCACCTGAACCATGGCTTTTCATGCTTCCAAGTGTCAGGGCCTTGCCCAGATAGACAGGGCTGACTCTGCTGCCC
4641  CAACCTTTCAAGGAGGAAACCAGACACCTGAGACAGGAGCCTGTATGCAGCCCAGTGCAGCCTTGCAGAGGACAAGGCTG
4721  GAGGCATTTGTCATCACTACAGATATGCAACTAAAATAGACGTGGAGCAAGAGAAATGCATTCCCACCGAGGCCGCTTTT
4801  TTAGGCCTAGTTGAAAGTCAAGAAGGACAGCAGCAAGCATAGGCTCAGGATTAAAGAAAAAAATCTGCTCACAGTCTGTT
4881  CTGGAGGTCACATCACCAACAAAGCTCACGCCCTATGCAGTTCTGAGAAGGTGGAGGCACCAGGCTCAAAAGAGGAAATT
4961  TAGAATTTCTCATTGGGAGAGTAAGGTACCCCCATCCCAGAATGATAACTGCACAGTGGCAGAACAAACTCCACCCTAAT
5041  GTGGGTGGACCCCATCCAGTCTGTTGAAGGCCTGAATGTAACAAAAGGGCTTATTCTTCCTCAAGTAAGGGGGAACTCCT
5121  GCTTTGGGCTGGGACATAAGTTTTTCTGCTTTCAGACGCAAACTGAAAAATGGCTCTTCTTGGGTCTTGAGCTTGCTGGC
5201  ATATGGACTGAAAGAAACTATGCTATTGGATCTCCTGGATCTCCAGCTTGCTGACTGCAGATCTTGAGATATGTCAGCCT
5281  CTACAGTCACAAGAGCTAATTCATTCTAATAAACCAATCTTTC
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FIGURE 18C-1

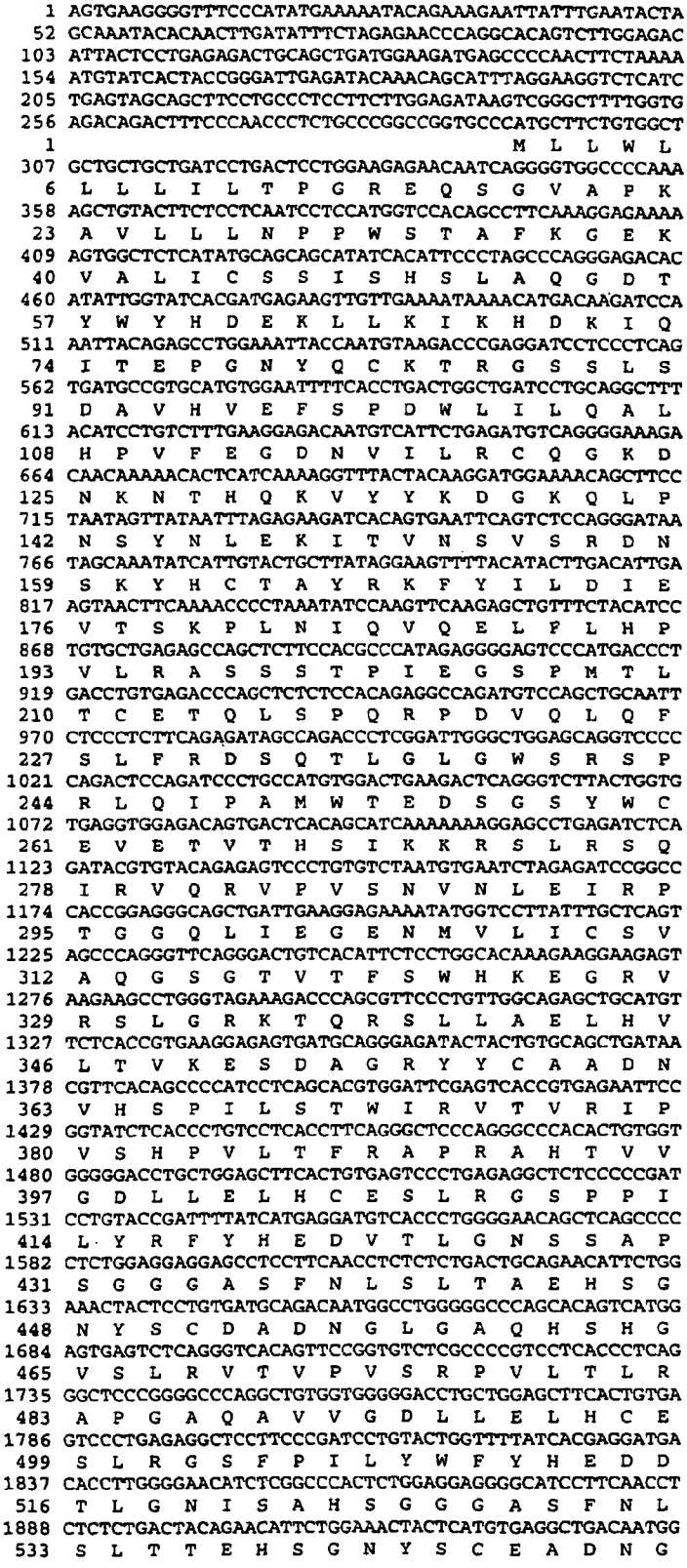
1 AGTGAAGGGGTTTCCCATATGAAAAATACAGAAAGAATTATTTGAATACTA
52 GCAAATACACAACTTGATATTTCTAGAGAACCCAGGCACAGTCTTGGAGAC
103 ATTACTCCTGAGAGACTGCAGCTGATGGAAGATGAGCCCCAACTTCTAAAA
154 ATGTATCACTACCGGGATTGAGATACAAACAGCATTTAGGAAGGTCTCATC
205 TGAGTAGCAGCTTCCTGCCCTCCTTCTTGGAGATAAGTCGGGCTTTTGGTG
256 AGACAGACTTTCCCAACCCTCTGCCCGGCCGGTGCCCATGCTTCTGTGGCT
1 M L L W L
307 GCTGCTGCTGATCCTGACTCCTGGAAGAGAACAATCAGGGGTGGCCCCAAA
6 L L L I L T P G R E Q S G V A P K
358 AGCTGTACTTCTCCTCAATCCTCCATGGTCCACAGCCTTCAAAGGAGAAAA
23 A V L L L N P P W S T A F K G E K
409 AGTGGCTCTCATATGCAGCAGCATATCACATTCCCTAGCCCAGGGAGACAC
40 V A L I C S S I S H S L A Q G D T
460 ATATTGGTATCACGATGAGAAGTTGTTGAAAATAAAACATGACAAGATCCA
57 Y W Y H D E K L L K I K H D K I Q
511 AATTACAGAGCCTGGAAATTACCAATGTAAGACCCGAGGATCCTCCCTCAG
74 I T E P G N Y Q C K T R G S S L S
562 TGATGCCGTGCATGTGGAATTTTCACCTGACTGGCTGATCCTGCAGGCTTT
91 D A V H V E F S P D W L I L Q A L
613 ACATCCTGTCTTTGAAGGAGACAATGTCATTCTGAGATGTCAGGGGAAAGA
108 H P V F E G D N V I L R C Q G K D
664 CAACAAAAACACTCATCAAAAGGTTTACTACAAGGATGGAAAACAGCTTCC
125 N K N T H Q K V Y Y K D G K Q L P
715 TAATAGTTATAATTTAGAGAAGATCACAGTGAATTCAGTCTCCAGGGATAA
142 N S Y N L E K I T V N S V S R D N
766 TAGCAAATATCATTGTACTGCTTATAGGAAGTTTTACATACTTGACATTGA
159 S K Y H C T A Y R K F Y I L D I E
817 AGTAACTTCAAAACCCCTAAATATCCAAGTTCAAGAGCTGTTTCTACATCC
176 V T S K P L N I Q V Q E L F L H P
868 TGTGCTGAGAGCCAGCTCTTCCACGCCCATAGAGGGGAGTCCCATGACCCT
193 V L R A S S S T P I E G S P M T L
919 GACCTGTGAGACCCAGCTCTCTCCACAGAGGCCAGATGTCCAGCTGCAATT
210 T C E T Q L S P Q R P D V Q L Q F
970 CTCCCTCTTCAGAGATAGCCAGACCCTCGGATTGGGCTGGAGCAGGTCCCC
227 S L F R D S Q T L G L G W S R S P
1021 CAGACTCCAGATCCCTGCCATGTGGACTGAAGACTCAGGGTCTTACTGGTG
244 R L Q I P A M W T E D S G S Y W C
1072 TGAGGTGGAGACAGTGACTCACAGCATCAAAAAAAGGAGCCTGAGATCTCA
261 E V E T V T H S I K K R S L R S Q
1123 GATACGTGTACAGAGAGTCCCTGTGTCTAATGTGAATCTAGAGATCCGGCC
278 I R V Q R V P V S N V N L E I R P
1174 CACCGGAGGGCAGCTGATTGAAGGAGAAAATATGGTCCTTATTTGCTCAGT
295 T G G Q L I E G E N M V L I C S V
1225 AGCCCAGGGTTCAGGGACTGTCACATTCTCCTGGCACAAAGAAGGAAGAGT
312 A Q G S G T V T F S W H K E G R V
1276 AAGAAGCCTGGGTAGAAAGACCCAGCGTTCCCTGTTGGCAGAGCTGCATGT
329 R S L G R K T Q R S L L A E L H V
1327 TCTCACCGTGAAGGAGAGTGATGCAGGGAGATACTACTGTGCAGCTGATAA
346 L T V K E S D A G R Y Y C A A D N
1378 CGTTCACAGCCCCATCCTCAGCACGTGGATTCGAGTCACCGTGAGAATTCC
363 V H S P I L S T W I R V T V R I P
1429 GGTATCTCACCCTGTCCTCACCTTCAGGGCTCCCAGGGCCCACACTGTGGT
380 V S H P V L T F R A P R A H T V V
1480 GGGGGACCTGCTGGAGCTTCACTGTGAGTCCCTGAGAGGCTCTCCCCCGAT
397 G D L L E L H C E S L R G S P P I
1531 CCTGTACCGATTTTATCATGAGGATGTCACCCTGGGGAACAGCTCAGCCCC
414 L Y R F Y H E D V T L G N S S A P
1582 CTCTGGAGGAGGAGCCTCCTTCAACCTCTCTCTGACTGCAGAACATTCTGG
431 S G G G A S F N L S L T A E H S G
1633 AAACTACTCCTGTGATGCAGACAATGGCCTGGGGGCCCAGCACAGTCATGG
448 N Y S C D A D N G L G A Q H S H G
1684 AGTGAGTCTCAGGGTCACAGTTCCGGTGTCTCGCCCCGTCCTCACCCTCAG
465 V S L R V T V P V S R P V L T L R
1735 GGCTCCCGGGGCCCAGGCTGTGGTGGGGGACCTGCTGGAGCTTCACTGTGA
483 A P G A Q A V V G D L L E L H C E
1786 GTCCCTGAGAGGCTCCTTCCCGATCCTGTACTGGTTTTATCACGAGGATGA
499 S L R G S F P I L Y W F Y H E D D
1837 CACCTTGGGGAACATCTCGGCCCACTCTGGAGGAGGGGCATCCTTCAACCT
516 T L G N I S A H S G G G A S F N L
1888 CTCTCTGACTACAGAACATTCTGGAAACTACTCATGTGAGGCTGACAATGG
533 S L T T E H S G N Y S C E A D N G

FIGURE 18C-2

```
1939 CCTGGGGGCCCAGCACAGTAAAGTGGTGACACTCAATGTTACAGGAACTTC
 550  L  G  A  Q  H  S  K  V  V  T  L  N  V  T  G  T  S
1990 CAGGAACAGAACAGGCCTTACCGCTGCGGGAATCACGGGGCTGGTGCTCAG
 567  R  N  R  T  G  L  T  A  A  G  I  T  G  L  V  L  S
2041 CATCCTCGTCCTTGCTGCTGCTGCTGCTCTGCTGCATTACGCCAGGGCCCG
 584  I  L  V  L  A  A  A  A  A  L  L  H  Y  A  R  A  R
2092 AAGGAAACCAGGAGGACTTTCTGCCACTGGAACATCTAGTCACAGTCCTAG
 601  R  K  P  G  G  L  S  A  T  G  T  S  S  H  S  P  S
2143 TGAGTGTCAGGAGCCTTCCTCGTCCAGGCCTTCCAGGATAGACCCTCAAGA
 618  E  C  Q  E  P  S  S  S  R  P  S  R  I  D  P  Q  E
2194 GCCCACTCACTCTAAACCACTAGCCCCAATGGAGCTGGAGCCAATGTACAG
 635  P  T  H  S  K  P  L  A  P  M  E  L  E  P  M  Y  S
2245 CAATGTAAATCCTGGAGATAGCAACCCGATTTATTCCCAGATCTGGAGCAT
 652  N  V  N  P  G  D  S  N  P  I  Y  S  Q  I  W  S  I
2296 CCAGCATACAAAAGAAAACTCAGCTAATTGTCCAATGATGCATCAAGAGCA
 669  Q  H  T  K  E  N  S  A  N  C  P  M  M  H  Q  E  H
2347 TGAGGAACTTACAGTCCTCTATTCAGAACTGAAGAAGACACACCCAGACGA
 686  E  E  L  T  V  L  Y  S  E  L  K  K  T  H  P  D  D
2398 CTCTGCAGGGGAGGCTAGCAGCAGAGGCAGGGCCCATGAAGAAGATGATGA
 703  S  A  G  E  A  S  S  R  G  R  A  H  E  E  D  D  E
2449 AGAAAACTATGAGAATGTACCACGTGTATTACTGGCCTCAGACCACTAGCC
 720  E  N  Y  E  N  V  P  R  V  L  L  A  S  D  H
2500 CCTTACCCAGAGTGGCCCACAGGAAACAGCCTGCACCATTTTTTTTTCTGT
2551 TCTCTCCAACCACACATCATCCATCTCTCCAGACTCTGCCTCCTACGAGGC
2602 TGGGCTGCAGGGTATGTGAGGCTGAGCAAAAGGTCTGCAAATCTCCCCTGT
2653 GCCTGATCTGTGTGTTCCCCAGGAAGAGAGCAGGCAGCCTCTGAGCAAGCA
2704 CTGTGTTATTTTCACAGTGGAGACACGTGGCAAGGCAGGAGGGCCCTCAGC
2755 TCCTAGGGCTGTCGAATAGAGGAGGAGAGAGAAATGGTCTAGCCAGGGTTA
2805 CAAGGGCACAATCATGACCATTTGATCCAAGTGTGATCGAAAGCTGTTAAT
2857 GTGCTCTCTGTATAAACAATTTGCTCCAAATATTTTGTTTCCCTTTTTTGT
2908 GTGGCTGGTAGTGGCATTGCTGATGTTTTGGTGTATATGCTGTATCCTTGC
2959 TACCATATTGGG
```

FIGURE 18D-1

```
   1 TGGTGACCAAGAGTACATCTCTTTTCAAATAGCTGGATTAGGTCCTCATGC
   1                                                 M  L
  52 TGCTGTGGTCATTGCTGGTCATCTTTGATGCAGTCACTGAACAGGCAGATT
  19   L  W  S  L  L  V  I  F  D  A  V  T  E  Q  A  D  S
 103 CGCTGACCCTTGTGGCGCCCTCTTCTGTCTTCGAAGGAGACAGCATCGTTC
  36   L  T  L  V  A  P  S  S  V  F  E  G  D  S  I  V  L
 154 TGAAATGCCAGGGAGAACAGAACTGGAAAATTCAGAAGATGGCTTACCATA
  53   K  C  Q  G  E  Q  N  W  K  I  Q  K  M  A  Y  H  K
 205 AGGATAACAAAGAGTTATCTGTTTTCAAAAAATTCTCAGATTTCCTTATCC
  70   D  N  K  E  L  S  V  F  K  K  F  S  D  F  L  I  Q
 256 AAAGTGCAGTTTTAAGTGACAGTGGTAACTATTTCTGTAGTACCAAAGGAC
  87   S  A  V  L  S  D  S  G  N  Y  F  C  S  T  K  G  Q
 307 AACTCTTTCTCTGGGATAAAACTTCAAATATAGTAAAGATAAAAGTCCAAG
 104   L  F  L  W  D  K  T  S  N  I  V  K  I  K  V  Q  E
 358 AGCTCTTTCAACGTCCTGTGCTGACTGCCAGCTCCTTCCAGCCCATCGAAG
 121   L  F  Q  R  P  V  L  T  A  S  S  F  Q  P  I  E  G
 409 GGGGTCCAGTGAGCCTGAAATGTGAGACCCGGCTCTCTCCACAGAGGTTGG
 138   G  P  V  S  L  K  C  E  T  R  L  S  P  Q  R  L  D
 460 ATGTTCAACTCCAGTTCTGCTTCTTCAGAGAAAACCAGGTCCTGGGGTCAG
 155   V  Q  L  Q  F  C  F  F  R  E  N  Q  V  L  G  S  G
 511 GCTGGAGCAGCTCTCCGGAGCTCCAGATTTCTGCCGTGTGGAGTGAAGACA
 172   W  S  S  S  P  E  L  Q  I  S  A  V  W  S  E  D  T
 562 CAGGGTCTTACTGGTGCAAGGCAGAAACGGTGACTCACAGGATCAGAAAAC
 189   G  S  Y  W  C  K  A  E  T  V  T  H  R  I  R  K  Q
 613 AGAGCCTCCAATCCCAGATTCACGTGCAGAGAATCCCCATCTCTAATGTAA
 206   S  L  Q  S  Q  I  H  V  Q  R  I  P  I  S  N  V  S
 664 GCTTGGAGATCCGGGCCCCCGGGGGACAGGTGACTGAAGGACAAAAACTGA
 223   L  E  I  R  A  P  G  G  Q  V  T  E  G  Q  K  L  I
 715 TCCTGCTCTGCTCAGTGGCTGGGGGTACAGGAAATGTCACATTCTCCTGGT
 240   L  L  C  S  V  A  G  G  T  G  N  V  T  F  S  W  Y
 766 ACAGAGAGGCCACAGGAACCAGTATGGGAAAGAAAACCCAGCGTTCCCTGT
 257   R  E  A  T  G  T  S  M  G  K  K  T  Q  R  S  L  S
 817 CAGCAGAGCTGGAGATCCCAGCTGTGAAAGAGAGTGATGCCGGCAAATATT
 274   A  E  L  E  I  P  A  V  K  E  S  D  A  G  K  Y  Y
 868 ACTGTAGAGCTGACAACGGCCATGTGCCTATCCAGAGCAAGGTGGTGAATA
 291   C  R  A  D  N  G  H  V  P  I  Q  S  K  V  V  N  I
 919 TCCCTGTGAGAATTCCAGTGTCTCGCCCTGTCCTCACCCTCAGGTCTCCTG
 308   P  V  R  I  P  V  S  R  P  V  L  T  L  R  S  P  G
 970 GGGCCCAGGCTGCAGTGGGGGACCTGCTGGAGCTTCACTGTGAGGCCCTGA
 325   A  Q  A  A  V  G  D  L  L  E  L  H  C  E  A  L  R
1021 GAGGCTCTCCCCCAATCTTGTACCAATTTTATCATGAGGATGTCACCCTTG
 342   G  S  P  P  I  L  Y  Q  F  Y  H  E  D  V  T  L  G
1072 GGAACAGCTCGGCCCCCTCTGGAGGAGGGGCCTCCTTCAACCTCTCTTTGA
 359   N  S  S  A  P  S  G  G  G  A  S  F  N  L  S  L  T
1123 CTGCAGAACATTCTGGAAACTACTCCTGTGAGGCCAACAACGGCCTGGGGG
 376   A  E  H  S  G  N  Y  S  C  E  A  N  N  G  L  G  A
1174 CCCAGTGCAGTGAGGCAGTGCCAGTCTCCATCTCAGGACCTGATGGCTATA
 393   Q  C  S  E  A  V  P  V  S  I  S  G  P  D  G  Y  R
1225 GAAGAGACCTCATGACAGCTGGAGTTCTCTGGGGACTGTTTGGTGTCCTTG
 410   R  D  L  M  T  A  G  V  L  W  G  L  F  G  V  L  G
1276 GTTTCACTGGTGTTGCTTTGCTGTTGTATGCCTTGTTCCACAAGATATCAG
 427   F  T  G  V  A  L  L  L  Y  A  L  F  H  K  I  S  G
1327 GAGAAAGTTCTGCCACTAATGAACCCAGAGGGGCTTCCAGGCCAAATCCTC
 444   E  S  S  A  T  N  E  P  R  G  A  S  R  P  N  P  Q
1378 AAGAGTTCACCTATTCAAGCCCAACCCCAGACATGGAGGAGCTGCAGCCAG
 461   E  F  T  Y  S  S  P  T  P  D  M  E  E  L  Q  P  V
1429 TGTATGTCAATGTGGGCTCTGTAGATGTGGATGTGGTTTATTCTCAGGTCT
 478   Y  V  N  V  G  S  V  D  V  D  V  V  Y  S  Q  V  W
1480 GGAGCATGCAGCAGCCAGAAAGCTCAGCAAACATCAGGACACTTCTGGAGA
 495   S  M  Q  Q  P  E  S  S  A  N  I  R  T  L  L  E  N
1531 ACAAGGACTCCCAAGTCATCTACTCTTCTGTGAAGAAATCATAACACTTGG
 512   K  D  S  Q  V  I  Y  S  S  V  K  K  S
1582 AGGAATCAGAAGGGAAGATCAACAGCAAGGATGGGGCATCATTAAGACTTG
1633 CTATAAAACCTTATGAAAATGCTTGAGGCTTATCACCTGCCACAGCCAGAA
1684 CGTGCCTCAGGAGGCACCTCCTGTCATTTTTGTCCTGATGATGTTTCTTCT
1735 CCAATATCTTCTTTTACCTATCAATATTCATTGAACTGCTGCTACATCCAG
1786 ACACTGTGCAAATAAATTATTTCTGCTACCTTCTCTTAAGCAATCAGTGTG
1837 TAAAGATTTGAGGGAAGAATGAATAAGAGATACAAGGTCTCACCTTCATCT
1888 ACTGTGAAGTGATGAGAACAGGACTTGATAGTGGTGTATTAACTTATTTAT
1939 GTGCTGCTGGATACAGTTTGCTAATATTTTGTTGAGAATTTTTGCAAATAT
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FIGURE 18D-2

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1990 GTTCATTGGGAATATTGGCCTGAAATTTTCTTTTCCACTGTGTCTCTGCCA
2041 GAATGTTTGTATCAGGCTGATGCTGGCTTCATAGAATGAGTTAGGCAGGAG
2092 CCCTTCCTCCTTGATTTTTTGGCATAGTTTCAGCAGGATTGGTACCAGTTA
2143 TTCTTTCTGCATCTTGTAGAATTCAGCTATGAATCCATCTGGTCTAGGGCT
2194 TTTGTGTTGGTTGGTAAGTTTTTTATTACTAATTCAACTTCAGCGCTTGAT
2245 ATTGGTCTAGGAGGGGTTTCTGTCTCTTCCTGGTTCAATCTTGGGAGATTG
2296 TGTGTTTCCAGGAATTTAGCCGTTTCCTCCAGATTTTCTTCTTTATGTGCA
2347 TCGACTTGAGTGTAAACATAACTTATATGCACTGGGAAACCAAAAAATCTG
2398 TGTGACTTGCTTTATTGCAGCATTTGTTTTATTTTGGTAGTCTGGAACTGA
2449 ACCTGCAATATCACCAAAGTATGCATATAGTTGCAAAAATGTGATTTTTGA
2500 CATAGTAAATATGAGTATTTGCAATAAACTATGATATTACTTTTGTAAGTA
2551 TATAGAATAAAATGTAAATAATCTATAAAA
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FIGURE 18E-1

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   1          GAGGCATCTCTAGGTACCATCCCTGACCTGGTCCTC
  37 ATGCTGCCGAGGCTGTTGCTGTTGATCTGTGCTCCACTCTGTGAA
     M  L  P  R  L  L  L  L  I  C  A  P  L  C  E
  82 CCTGCCGAGCTGTTTTTGATAGCCAGCCCCTCCCATCCCACAGAG
     P  A  E  L  F  L  I  A  S  P  S  H  P  T  E
 127 GGGAGCCCAGTGACCCTGACGTGTAAGATGCCCTTTCTACAGAGT
     G  S  P  V  T  L  T  C  K  M  P  F  L  Q  S
 172 TCAGATGCCCAGTTCCAGTTCTGCTTTTTCAGAGACACCCGGGCC
     S  D  A  Q  F  Q  F  C  F  F  R  D  T  R  A
 217 TTGGGCCCAGGCTGGAGCAGCTCCCCCAAGCTCCAGATCGCTGCC
     L  G  P  G  W  S  S  S  P  K  L  Q  I  A  A
 262 ATGTGGAAAGAAGACACAGGGTCATACTGGTGCGAGGCACAGACA
     M  W  K  E  D  T  G  S  Y  W  C  E  A  Q  T
 307 ATGGCGTCCAAAGTCTTGAGGAGCAGGAGATCCCAGATAAATGTG
     M  A  S  K  V  L  R  S  R  R  S  Q  I  N  V
 352 CACAGGGTCCCTGTCGCTGATGTGAGCTTGGAGACTCAGCCCCCA
     H  R  V  P  V  A  D  V  S  L  E  T  Q  P  P
 397 GGAGGACAGGTGATGGAGGGAGACAGGCTGGTCCTCATCTGCTCA
     G  G  Q  V  M  E  G  D  R  L  V  L  I  C  S
 442 GTTGCTATGGGCACAGGAGACATCACCTTCCTTTGGTACAAAGGG
     V  A  M  G  T  G  D  I  T  F  L  W  Y  K  G
 487 GCTGTAGGTTTAAACCTTCAGTCAAAGACCCAGCGTTCACTGACA
     A  V  G  L  N  L  Q  S  K  T  Q  R  S  L  T
 532 GCAGAGTATGAGATTCCTTCAGTGAGGGAGAGTGATGCTGAGCAA
     A  E  Y  E  I  P  S  V  R  E  S  D  A  E  Q
 577 TATTACTGTGTAGCTGAAAATGGCTATGGTCCCAGCCCCAGTGGG
     Y  Y  C  V  A  E  N  G  Y  G  P  S  P  S  G
 622 CTGGTGAGCATCACTGTCAGAATCCCGGTGTCTCGCCCAATCCTC
     L  V  S  I  T  V  R  I  P  V  S  R  P  I  L
 667 ATGCTCAGGGCTCCCAGGGCCCAGGCTGCAGTGGAGGATGTGCTG
     M  L  R  A  P  R  A  Q  A  A  V  E  D  V  L
 712 GAGCTTCACTGTGAGGCCCTGAGAGGCTCTCCTCCAATCCTGTAC
     E  L  H  C  E  A  L  R  G  S  P  P  I  L  Y
 757 TGGTTTTATCACGAGGATATCACCCTGGGGAGCAGGTCGGCCCCC
     W  F  Y  H  E  D  I  T  L  G  S  R  S  A  P
 802 TCTGGAGGAGGAGCCTCCTTCAACCTTTCCCTGACTGAAGAACAT
     S  G  G  G  A  S  F  N  L  S  L  T  E  E  H
 847 TCTGGAAACTACTCCTGTGAGGCCAACAATGGCCTGGGGGCCCAG
     S  G  N  Y  S  C  E  A  N  N  G  L  G  A  Q
 892 CGCAGTGAGGCGGTGACACTCAACTTCACAGTGCCTACTGGGGCC
     R  S  E  A  V  T  L  N  F  T  V  P  T  G  A
 937 AGAAGCAATCATCTTACCTCAGGAGTCATTGAGGGGCTGCTCAGC
     R  S  N  H  L  T  S  G  V  I  E  G  L  L  S
 982 ACCCTTGGTCCAGCCACCGTGGCCTTATTATTTTGCTACGGCCTC
     T  L  G  P  A  T  V  A  L  L  F  C  Y  G  L
1027 AAAAGAAAAATAGGAAGACGTTCAGCCAGGGATCCACTCAGGAGC
     K  R  K  I  G  R  R  S  A  R  D  P  L  R  S
1072 CTTCCCAGCCCTCTACCCCAAGAGTTCACCTACCTCAACTCACCT
     L  P  S  P  L  P  Q  E  F  T  Y  L  N  S  P
1117 ACCCCAGGGCAGCTACAGCCTATATATGAAAATGTGAATGTTGTA
     T  P  G  Q  L  Q  P  I  Y  E  N  V  N  V  V
1162 AGTGGGGATGAGGTTTATTCACTGGCGTACTATAACCAGCCGGAG
     S  G  D  E  V  Y  S  L  A  Y  Y  N  Q  P  E
1207 CAGGAATCAGTAGCAGCAGAAACCCTGGGGACACATATGGAGGAC
     Q  E  S  V  A  A  E  T  L  G  T  H  M  E  D
1252 AAGGTTTCCTTAGACATCTATTCCAGGCTGAGGAAAGCAAACATT
     K  V  S  L  D  I  Y  S  R  L  R  K  A  N  I
1297 ACAGATGTGGACTATGAAGATGCTATGTAA 1326
     T  D  V  D  Y  E  D  A  M  *
                                    GGTT ATGGAAGATT CTGCTCTTTG
1351 AAAACCATCC ATGACCCCAA GCCTCAGGCC TGATATGTTC TTCAGAGATC
1401 CTGGGGCATT AGCTTTCCAG TATACCTCTT CTGGATGCCA TTCTCCATGG
1451 CACTATTCCT TCATCTACTG TGAAGTGAAG TTGGCGCAGC CCTGAAGAAA
1501 CTACCTAGGA GAACTAATAG ACACAGGAGT GACAGGGACT TTGTTATCAG
1551 AACCAGATTC CTGCCGGCTC CTTTGAAAAC AGGTCATATT GTGCTCTTCT
1601 GTTTACAAGA GGAAACAAGA TGGAATAAAA GAAATTGGGA TCTTGGGTTG
1651 GAGGGACAGT GAAGCTTAGA GCACATGAAC TCAAGGTTAG TGACTCTGCA
1701 GGACTTCACA GAGAGAGCTG TGCCCATCAT TCAGTCCAAG TGCTTTCTCT
1751 GCCCAGACAG CACAGAACTC CAGCCCCGCT ACTTACATGG ATCATCGAGT
1801 TTCCACCTAA AATATGATTC TATTTATTTT GAGTCACTGT TACCAAATTA
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FIGURE 18E-2

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1851  GAACTAAAAC AAAGTTACAT AAAAAGTTAT TGTGACTCCA CTTAATTTTA
1901  GTGACGTATT TTTGTATATA TAGGCCAACC TATACCACAT CCAAAATTAT
1951  GTATCTATTA CAGCCCCTAG AAGCTTTATA AATACAGTGT GTCTTCTTTT
2001  ATTCACAAAA TTTTTGAAAT CGTGGTAATA TGGTTTGAAA CCTGTATCTT
2051  AATTATTTTT TTTTTAAATT GAGACAGGGT CTCACTCTGT CACTCAATCT
2101  GGAATGCAGT GGCACAATCT TGCCTCACTG CAACGCCTGC CTCTCAGGCT
2151  CAAGCAAACC TCTCACCTCA GCCTGCTGAG TAGCTGGGAC TACAGGCACA
2201  TGCCACCAAA CTTGGCCATT TTTTGTCTTA CGTAGAGACA AGATTTCACC
2251  GTTTTGCCCA GGCTGGTCTC AAACTCCTGG GCTCAAGCAA TGTATTGAAT
2301  TTT
```

ISOLATION OF FIVE NOVEL GENES CODING FOR NEW FC RECEPTORS-TYPE MELANOMA INVOLVED IN THE PATHOGENESIS OF LYMPHOMA/MELANOMA

This application is a continuation of U.S. Ser. No. 09/724,254, filed Nov. 28, 2000, now U.S. Pat. No. 7,105,149, which claims benefit of U.S. Provisional Application Ser. No. 60/168,151, filed Nov. 29, 1999, the contents of which are hereby incorporated by reference into the present application.

The invention disclosed was herein made in the course of work under NCI Grant No. CA 44029 from the National Cancer Institute. Accordingly, the U.S. Government has certain rights in this invention.

Throughout this application, various references are referred to in parentheses. Disclosures of these publication in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains. Full bibliographic citation for these references may be found at the end of this application, preceding the claims.

BACKGROUND OF THE INVENTION

Abnormalities of chromosome 1q21 are common in B cell malignancies, including B cell lymphoma and myeloma, but the genes targeted by these aberrations are largely unknown. By cloning the breakpoints of a t(11;14)(q21;q32) chromosomal translocation in a myeloma cell line, we have identified two novel genes, IRTA1 and IRTA2, encoding cell surface receptors with homologies to the Fc and Inhibitory Receptor families. Both genes are normally expressed in mature B cells, but with different distributions in peripheral lymphoid organs: IRTA1 is expressed in marginal zone B cells, while IRTA2 is also expressed in germinal center centrocytes and in immunoblasts. As the result of the t(1;14) translocation, the IRTA1 signal peptide is fused to the Immunoglobulin Ca domain to produce a chimaeric IRTA1/Ca fusion protein. In Multiple Myeloma and Burkitt lymphoma cell lines with 1q21 abnormalities, IRTA2 expression is deregulated. Thus, IRTA1 and IRTA2 are novel immunoreceptors with a potentially important role in B cell development and lymphomagenesis.

B-cell Non-Hodgkin's Lymphoma (B-NHL) and Multiple Myeloma (MM) represent a heterogeneous group of malignancies derived from mature B cells with phenotypes corresponding to pre-Germinal Center (GC) (mantle cell), GC (follicular, diffuse large cell, Burkitt's), or post-GC B cells (MM) (for review, Gaidano and Dalla-Favera, 1997; Kuppers et al., 1999). Insights into the pathogenesis of these malignancies have been gained by the identification of recurrent clonal chromosomal abnormalities characteristic for specific disease subtypes. The common consequence of these translocations is the transcriptional deregulation of protooncogenes by their juxtaposition to heterologous transcriptional regulatory elements located in the partner chromosome (Gaidano and Dalla-Favera, 1997). These heterologous transcriptional regulatory elements can be derived from the Immunoglobulin (IG) locus or from other partner chromosomal loci. Examples include MYC in t(8;14) (q24;q32) in Burkitt's lymphoma (BL) (Dalla-Favera et al., 1982; Taub et al., 1982), the CCND1 gene deregulated by the t(11;14)(q13;q32) in mantle cell lymphoma (MCL) (Rosenberg et al., 1991) and multiple myeloma (MM) (Ronchetti et al., 1999), BCL2 involved in the t(14;18) (q32;q21) in follicular lymphoma (FL) (Bakhshi et al., 1985), BCL6 in t(3;14) (q27;q32) in diffuse large B cell lymphoma (DLCL) (Ye et al., 1993), as well as FGFR3 in t(4;14) (p16;q32) (Chesi et al., 1997), MAF in t(14;16) (q32;q23) (Chesi et al., 1998) and MUM1/IRF4 in t(6;14) (p25;q32) (Iida et al., 1997) in multiple myeloma (MM). The identification of these oncogenes has offered valuable insights into the pathogenesis and diagnosis of their corresponding malignancies.

Chromosomal abnormalities involving band 1q21-q23 are among the most frequent genetic lesions in both B-NHL and MM. Among NHL subtypes, translocation breakpoints at 1q21-q23, including translocations and duplications, have been reported, often as the single chromosomal abnormality, in 17-20% of follicular and diffuse large B-cell lymphoma (DLCL), in 39% of marginal-zone B cell lymphoma (Offit et al., 1991; whang-Peng et al., 1995; Cigudosa et al., 1999) and in 27-38% of Burkitt lymphoma, where they represent the second most common cytogenetic abnormality after translocations involving the MYC proto-oncogene (Berger and Bernheim, 1985; Kornblau et al., 1991). Comparative genome hybridization (CGH) has also identified 1q21-q23 as a recurring site for high-level amplification in 10% of DLCL cases (Rao et al., 1998). In MM, trisomy of the 1q21-q32 region has been reported in 20-31% of cases (Sawyer et al., 1995), amplification of the 1q12-qter region in 80% of cell lines and 40% of primary tumors (Avet-Loiseau et al., 1997), and nonrandom unbalanced whole-arm translocations of 1q, associated with the multiduplication of the adjacent 1q21-22 region, were found in 23% of patients with abnormal karyotypes (Sawyer et al., 1998).

The high frequency of involvement of 1q21 structural rearrangements in B-cell malignancies suggests that this locus may harbor genes critical to the pathogenesis of these diseases. Cloning of a t(1;14) (q21;q32) in a pre-B cell acute lymphoblastic leukemia cell line previously identified a novel gene, BCL9 deregulated in this single case (Willis et al., 1998), but not involved in other cases. A recent report characterized the t(1;22) (q22;q11) in a follicular lymphoma (FL) cell line and found that the FCGR2B locus, encoding the low affinity IgG Fc receptor FCGRIIB, was targeted in this cell line and in two additional FL cases (Callanan et al., 2000). Finally, the MUC1 locus has been identified in proximity of the breakpoint of a t(1;14) (q21;q32) in NHL (Dyomin et al., 2000; Gilles et al., 2000), and MUC1 locus rearrangements have been found in 6% of NHL with 1q21 abnormalities (Dyomin et al., 2000). These results highlight the heterogeneity of the 1q21 breakpoints and the need to identify additional candidate oncogenes situated in this locus, since the large majority of these alterations remain unexplained.

The aim of this study was to further explore the architecture of 1q21 chromosomal rearrangements in B cell malignancy. To that end, we have employed a molecular cloning approach of the t(1;14) (q21;q32) present in the myeloma cell line FR4. We have identified two novel genes that are differentially targeted by 1q21 abnormalities. These genes code for five novel members of the immunoglobulin receptor family, IRTA1, IRTA2, IRTA3, IRTA4 and IRTA5 (Immunoglobulin superfamily Receptor Translocation Associated genes 1, 2, 3, 4, and 5), which may be important for normal lymphocyte function and B cell malignancy.

SUMMARY OF THE INVENTION

This invention provides an isolated nucleic acid molecule which encodes immunoglobulin receptor, Immunoglobulin superfamily Receptor Translocation Associated, IRTA, protein.

This invention provides a method of producing an IRTA polypeptide (protein) which comprises: (a) introducing a vector comprising an isolated nucleic acid which encodes an immunoglobulin receptor, Immunoglobulin superfamily Receptor Translocation Associated, IRTA, protein into a suitable host cell; and (b) culturing the resulting cell so as to produce the polypeptide.

This invention provides an isolated nucleic acid molecule comprising at least 15 contiguous nucleotides capable of specifically hybridizing with a unique sequence included within the sequence of the isolated nucleic acid molecule encoding IRTA protein. In an embodiment, the IRTA protein may be IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 protein, or fragment(s) thereof, having the amino acid sequence set forth in any of FIGS. **18**A (SEQ ID NO:1), **18**B-**1**-**18**B-**3** (SEQ ID NOs:3, 41, 44), **18**C-**1**-**18**C-**2** (SEQ ID NO:5), **18**D-**1**-**18**D-**2** (SEQ ID NO:7) or **18**E-**1**-**18**E-**2** (SEQ ID NO:9), respectively.

This invention provides a method for detecting a B cell malignancy or a type of B cell malignancy in a sample from a subject wherein the B cell malignancy comprises a 1q21 chromosomal rearrangement which comprises: a) obtaining RNA from the sample from the subject; b) contacting the RNA of step (a) with a nucleic acid molecule of at least 15 contiguous nucleotides capable of specifically hybridizing with a unique sequence included within the sequence of an isolated RNA encoding human IRTA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9), under conditions permitting hybridization of the RNA of step (a) with the nucleic acid molecule capable of specifically hybridizing with a unique sequence included within the sequence of an isolated RNA encoding human IRTA protein, wherein the nucleic acid molecule is labeled with a detectable marker; and c) detecting any hybridization in step (b), wherein detection of hybridization indicates presence of B cell malignancy or a type of B cell malignancy in the sample.

This invention provides an antisense oligonucleotide having a sequence capable of specifically hybridizing to an mRNA molecule encoding a human IRTA protein so as to prevent overexpression of the mRNA molecule.

This invention provides a purified IRTA1 protein comprising the amino acid sequence set forth in FIG. **18**A (SEQ ID NO:1).

This invention provides a purified IRTA2 protein comprising an amino acid sequence set forth in FIGS. **18**B-**1**-**18**B-**3** (SEQ ID NO:41, SEQ ID NO:3, SEQ ID NO:44).

This invention provides a purified IRTA3 protein comprising the amino acid sequence set forth in FIGS. **18**C-**1**-**18**C-**2** (SEQ ID NO:5).

This invention provides a purified IRTA4 protein comprising the amino acid sequence set forth in FIGS. **18**D-**1**-**18**D-**2** (SEQ ID NO: 7).

This invention provides a purified IRTA5 protein comprising the amino acid sequence set forth in FIGS. **18**E-**1**-**18**E-**2** (SEQ ID NO: 9).

This invention provides an antibody/antibodies directed to an epitope of a purified IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 protein, or fragment(s) thereof, having the amino acid sequence set forth in any of FIGS. **18**A (SEQ ID NO:1), **18**B-**1**-**18**B-**3** (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), **18**C-**1**-**18**C-**2** (SEQ ID NO:5), **18**D-**1**-**18**D-**2** (SEQ ID NO:7) or **18**E-**1**-**18**E-**2** (SEQ ID NO:9), respectively.

This invention provides an antibody directed to a purified IRTA protein selected from the group consisting of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9).

This invention provides a pharmaceutical composition comprising an amount of the antibody directed to an IRTA protein effective to bind to cancer cells expressing an IRTA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9), so as to prevent growth of the cancer cells and a pharmaceutically acceptable carrier.

This invention provides a pharmaceutical composition comprising an amount of any of the oligonucleotides of nucleic acid molecules encoding IRTA proteins described herein effective to prevent overexpression of a human IRTA protein and a pharmaceutically acceptable carrier capable.

This invention provides a method of diagnosing B cell malignancy which comprises a 1q21 chromosomal rearrangement in a sample from a subject which comprises: a) obtaining the sample from the subject; b) contacting the sample of step (a) with an antibody directed to a purified IRTA protein capable of specifically binding with a human IRTA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) IRTA protein on a cell surface of a cancer cell under conditions permitting binding of the antibody with human IRTA protein on the cell surface of the cancer cell, wherein the antibody is labeled with a detectable marker; and c) detecting any binding in step (b), wherein detection of binding indicates a diagnosis of B cell malignancy in the sample.

This invention provides a method of detecting human IRTA protein in a sample which comprises: a) contacting the sample with any of any of the above-described anti-IRTA antibodies under conditions permitting the formation of a complex between the antibody and the IRTA in the sample; and b) detecting the complex formed in step (a), thereby detecting the presence of human IRTA in the sample.

This invention provides a method of treating a subject having a B cell cancer which comprises administering to the subject an amount of anti-IRTA antibody effective to bind to cancer cells expressing an IRTA protein so as to prevent growth of the cancer cells and a pharmaceutically acceptable carrier, thereby treating the subject.

This invention provides a method of treating a subject having a B cell cancer which comprises administering to the subject an amount of an antisense oligonucleotide having a sequence capable of specifically hybridizing to an mRNA molecule encoding a human ITRA protein so as to prevent overexpression of the human IRTA protein, so as to arrest cell growth or induce cell death of cancer cells expressing IRTA protein(s) and a pharmaceutically acceptable carrier, thereby treating the subject.

The invention also provides a pharmaceutical composition comprising either an effective amount of any of the oligonucleotides described herein and a pharmaceutically acceptable carrier.

The invention also provides a pharmaceutical composition comprising either an effective amount of an antibody directed against an epitope of any IRTA protein described herein and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE FIGURES

FIGS. **1**A-**1**B. Molecular cloning of the translocation t(1;14)(q21;q32) in the FR4 multiple myeloma cell line. FIG. **1**A) Schematic representation of the λFR4B-5 and λFR4S-a

clones, representing der(14) and der(1) breakpoints, and of the germline IgH and 1q21 loci. FIG. **1**B) Nucleotide sequence of the breakpoint junction (SEQ ID NO:12) and its alignment to the corresponding germline regions of chromosome 14 (SEQ ID NO:13). Chr 1 is SEQ ID NO:11. Sα, IgA switch region; LCR: 3' IgH locus control region; B, BamHI; H, HindIII; X, XhoI.

FIGS. **2**A-**2**B. Genomic map of the 1q21 locus in the vicinity of the FR4 breakpoint. FIG. **2**A) Restriction endonuclease map and schematic representation of genomic clones, i.e. bacteriophages (1), P1 artificial chromosomes (PACs) (2), and yeast artificial chromosome (YAC) (3), spanning the germline 1q21 locus at the FR4 breakpoint region (arrowhead). The name of each clone is placed directly on top of its representation. End fragments derived from the PAC and YAC inserts are depicted as circles, with either an SP6/T7 vector orientation (PAC), or left/right arm vector orientation (YAC). The top panel in FIG. **1**A depicts the genomic organization of two genes surrounding the FR4 breakpoint. The two genes were identified by exon trapping of PAC 49A16. They are closely spaced in the genome, within ≦30 Kb of each other and are named MUM2 and MUM3 (multiple myeloma-2 and 3). In the scheme of their genomic loci, black boxes indicate coding exons, whereas white and light or medium grey boxes indicate non-coding exons. Connecting introns are lines. MUM3 (left) gives rise to three alternatively spliced mRNAs, all sharing a common 5' untranslated region (UTR) but diverse 3' UTRs (marked by different shades). Numbers underneath the boxes identify the order of exons in the cDNA. Exons less than 100 bp are depicted as thin vertical lines. The position and size of each exon was determined by sequencing of genomic PAC and phage clones and by hybridization of cDNA probes to endonuclease-digested clone DNA. PAC and YAC mapping was performed by partial digestion with rare cutting enzymes followed by Pulse-Field-Gel-Electrophoresis and hybridization to internal and end-derived probes. Dashed lines align regions of overlap. S, SacI; H, HindIII; S, SwaI; Pc, PacI; P, PmeI; FIG. **2**B) Genethon genetic linkage map of 1q21 in the region of the MUM2/MUM3 locus. Sequence-tagged sites (STS) are ordered in approximate distance previously determined by Dib, C., et al. (1996) *Nature,* 380:162-164. STS WI-5435 (in bold) is contained within YAC 23GC4 and PAC 49A16. Parallel vertical lines represent interrupted segments, whose approximate size is depicted above in megabases (MB). Sizing was estimated by the size of nonchimeric YAC contigs between two markers. The BCL9 gene at the centromere was cloned from a different t(1;14)(q21;q32) breakpoint by Willis T. G. et al., (1998) *Blood* 91, 6:1873-1881. The FcGRIIA gene is at the 1q21-q22 chromosomal band border.

FIGS. **3**A-**3**C. MUM2 mRNA structure and expression pattern. FIG. **3**A) Schematic representation of MUM2 mRNA. Pattern-filled, wide boxes represent coding domains and narrow empty boxes represent untranslated regions. SP, signal peptide; EC, extracellular domain; TM, transmembrane domain; CYT, cytoplasmic domain; A(n), polyA tail. The extracellular region is composed of four immunoglobulin-like domains as depicted. Alternative polyadenylation signals (arrows) generate three MUM2 mRNA species (a, b, c) whose length (in Kb) ranges from 2.6-3.5. FIG. **3**B) Northern blot analysis of MUM2 mRNA expression in human tissues of the immune system. The cDNA probe used for the analysis is shown as a solid bar underneath the mRNA scheme in FIG. **3**A). Each lane contains 21 g mRNA of the corresponding tissue. On the right side of the blot, the position of RNA molecular weight markers is depicted. The position of MUM2 and GAPDH mRNA transcripts is shown by arrows. (A GAPDH probe was included in the hybridization as an internal control—0.15 ng labelled+50 ng unlabelled probe—). The results of this analysis show weak expression of MUM2 in lymph node and spleen. MUM2 expression was not detected in a variety of other human tissues (data not shown). FIG. **3**C) Northern blot analysis of MUM2 expression in total RNA from EREB, a conditional EBV-transformed B lymphoblastoid cell line. EREB carries the EBV genome with an EBNA2-estrogen receptor fusion protein, active only in the presence of estrogen. For this experiment, cells were grown in the presence of estrogen (1 μg/ml), followed by estrogen withdrawal for the indicated times. Upon estrogen withdrawal, EREB cells undergo G0/G1 arrest, determined by the loss of c-myc expression. In FIG. **3**C, a Northern blot of EREB total RNA (10 μg per lane) was hybridized with the MUM2 cDNA probe shown in FIG. **3**A and the GAPDH internal control probe, as in FIG. **3**B. Arrows indicate the position of the corresponding mRNAs on the EREB blot. a, band c correspond to the MUM2 species in panel FIG. **3**A. The same blot was then stripped and reprobed with a c-myc cDNA probe (exon 2) to verify cellular G0/G1 arrest. Quantitation of MUM2 mRNA by the use of a phosphorimager densitometric analysis demonstrates a 10-fold increase in their levels within 48 hrs of estrogen withdrawal, suggesting that MUM2 expression is elevated as the cells enter a resting phase.

FIGS. **4**A-**4**B. MUM3 mRNA structure and expression pattern. FIG. **4**A) Schematic representation of MUM3 mRNA Pattern-filled, wide boxes represent coding domains and narrow empty or gray boxes represent untranslated regions. SP, signal peptide; EC, extracellular domain; TM, transmembrane domain; CYT, cytoplasmic domain; A(n), polyA tail. The extracellular region is composed of immunoglobulin-like domains, as depicted. Alternative splicing generates four mRNA species with diverse subcellular localization. MUM3-a and -d proteins are secreted, whereas MUM3-b contains a hydrophobic stretch of amino acids at its C-terminus which may serve as a signal for addition of a glycophosphatidyl-inositol anchor (GPI-anchor), as shown. MUM3-c spans the plasma membrane. Sequence identity among species is indicated by identical filling. FIG. **4**B) Northern blot analysis of MUM3 mRNA expression in multiple human tissues (left) and in various lymphoid and non-lymphoid cell lines (right). The cDNA probe used is shown as a solid bar below the cDNA scheme in FIG. **4**A. Each lane contains 2 μg mRNA of the corresponding tissue or cell line. The position of MUM3 and GAPDH mRNA transcripts is shown by arrows. (A GAPDH probe was included in the hybridization as an internal control as described in FIG. **3**) a, b, c and d correspond to the MUM3 mRNA species shown in FIG. **4**A. RD, NC42 and CB33, Epstein-Barr virus transformed B lymphoblastoid cell lines; EREB, conditional EBV-transformed B lymphoblastoid cell line; FR4, plasma cell line; MOLT4 and HUT78, T cell lines; HL60 and U937, myelomonocytic cell lines; K562, erythroid cell line. The results suggest that MUM3 is expressed solely in the immune system tissues of bone marrow, lymph and spleen and in particular in B cells with a lymphoblastoid phenotype.

FIG. **5**. Nucleotide and amino acid sequence of human MUM2 (SEQ ID NO:14 and SEQ ID NO:15, respectively). The deduced amino acid sequence is shown above the nucleotide sequence in one-letter code and is numbered on the right, with position 1 set to the first codon of the signal peptide. The predicted signal peptidase site was derived by a computer algorithm described in Nielsen et al., *Protein Engineering* 10, 1-6 (1997) and is marked by an arrowhead. The polyadenylation signal AATAAA is underlined. Potential

sites for N-glycosylation are also underlined in the amino acid sequence. A hydrophobic stretch of 16 amino acids predicted to span the plasma membrane is doubly underlined. Consensus SH2-binding sites are highlighted by a wavy underline.

FIG. **6**A. Nucleotide and amino acid sequence of human MUM3-a (SEQ ID NO:16 and SEQ ID NO:17, respectively). The deduced amino acid sequence is shown above the nucleotide sequence in one-letter code and is numbered on the right, with position 1 set to the first codon of the signal peptide. The predicted site for signal peptidase cleavage was derived as previously stated above and is marked by an arrowhead. The polyadenylation signal ATTAAA is underlined. Potential sites for N-glycosylation are also underlined in the amino acid sequence. The protein lacks a transmembrane domain and is predicted to be secreted.

FIG. **6**B. Nucleotide and amino acid sequence of human MUM3-b (SEQ ID NO:18 and SEQ ID NO:19, respectively). The deduced amino acid sequence is shown above the nucleotide sequence in one-letter code and is numbered on the right, with position 1 set to the first codon of the signal peptide. The predicted site for signal peptidase cleavage was derived as previously stated above and is marked by an arrowhead. The polyadenylation signal AATAAA is underlined. Potential sites for N-glycosylation are underlined in the amino acid sequence.

FIGS. **6**C-**1**-**6**C-**2**. Nucleotide and amino acid sequence of human MUM3-c (SEQ ID NO:20 and SEQ ID NO:21, respectively). The deduced amino acid sequence is shown above the nucleotide sequence in one-letter code and is numbered on the right, with position 1 set to the first codon of the signal peptide. The predicted site for signal peptidase cleavage was derived as previously stated above and is marked by an arrowhead. The polyadenylation signal AATAAA is underlined. Potential sites for N-glycosylation are underlined in the amino acid sequence. A hydrophobic stretch of 23 amino acids predicted to span the plasma membrane is doubly underlined. Consensus SH2-binding sites are highlighted by a wavy underline.

FIGS. **7**A-**7**C. t(1;14)(q21;32) in FR4 generates a MUM2/Ca fusion transcript. (FIG. **7**A) Schematic representation of ther der(14) genomic clone λFR4B-5 and of the germline IgHA1 locus. The FR4 breakpoint is marked by an arrow. Filled and open boxes represent the MUM2 and Calpha coding and non-coding exons respectively. The position of the MUM2 exon 1 probe used for Northern blot analysis is shown by a bar. (FIG. **7**B) Northern blot analysis with a MUM2 exon 1 probe on FR4 and additional cell lines detects an abnormal message of 0.8 Kb, selectively in FR4. Arrowheads point to the location of normal MUM2 message in EREB mRNA. JJN3 and U266, myeloma cell lines; EREB, conditional EBV-transformed B lymphoblastoid cell line. Two μg of polyA+ RNA were loaded per lane. (FIG. **7**C) Nucleotide and amino acid sequence of the MUM2-Ca fusion cDNA in FR4 (SEQ ID NO:23 and SEQ ID NO:22, respectively). The cDNA was amplified by RT-PCR from FR4 total RNA using the primers shown in FIG. **7**A, and was subsequently subcloned and sequenced. The deduced amino acid sequence is shown above the nucleotide sequence in one-letter code and is numbered on the right with position 1 set to the first codon of the signal peptide. The predicted site for signal peptidase cleavage was derived as previously stated above and is marked by an arrowhead. The polyadenylation signal AATAAA is underlined. The Calpha transmembrane domain is underlined. The MUM2 portion of the cDNA is shown on italics. H, HindIII; B, BamHI; X, XhoI; Sα, IgA switch region; EC, extracellular region; TM, transmembrane; CYT, cytoplasmic domain.

FIGS. **8**A-**8**C. Molecular cloning of the translocation t(1;14)(q21;q32) in the FR4 multiple myeloma cell line. (FIG. **8**A) Schematic representation of the phage clones representing der(14) and der(1) breakpoints and the germline IGH and 1q21 loci. Chromosome 14 sequences are indicated by a solid black line with black boxes representing Ca1 exons. Chromosome 1 sequences are shown as a grey line. The probes used for chromosomal mapping are indicated below the map. Restriction enzyme codes are: B, BamHI; H, HindIII; X, XhoI; S, SacI; E, EcoRI. For enzymes marked by (*) only sites delineating the probes are shown. Sa: IgA switch region; LCR: 3'IgH locus control region. (FIG. **8**B) Nucleotide sequence of the breakpoint junctions (SEQ ID NO:25 and SEQ ID NO:27) and their alignment to the corresponding germline regions of chromosomes 14 and 1 (SEQ ID NO:24 and SEQ ID NO:26, respectively). (FIG. **8**C) Left, fluorescence in situ hybridization (FISH) analysis on human normal metaphase spreads with the PAC clone 49A16 (FIG. **13**) spanning the germline1q21 region at the FR4 breakpoint. Right, DAPI stained image from the same metaphase spread.

FIGS. **9**A-**9**B. Structure of IRTA1 and IRTA2 cDNAs. FIGS. **9**A,**9**B) Schematic representation of the full-length IRTA1 (FIG. **9**A) and IRTA2 (FIG. **9**B) cDNAs. Pattern-filled, wide boxes represent coding domains and narrow boxes represent untranslated regions (UTR). The predicted site for signal peptidase cleavage is marked by an arrowhead and was derived according to the SignalIP World Wide Web-server at http://www.cbs.dtu.dk/services/SignalIP. The transmembrane domain prediction algorithm is described in Tusnady et al, 1998. SP, signal peptide; EC, extracellular domain; Ig, immuno-globulin-type; TM, transmembrane domain; CYT, cytoplasmic domain; A(n), polyA tail; GPI, glycophosphatidyl inositol. In (FIG. **9**A), arrows in the 3' UTR indicate different polyadenylation addition sites utilized in the IRTA1 cDNA. In (FIG. **9**B), different 3'UTR regions in IRTA2 isoforms are differentially shaded. Bars underneath the UTR regions in (FIG. **9**A) and (FIG. **9**B) identify probes used for Northern blot analysis in FIG. **12**.

FIGS. **10**A-**10**B. Comparison of the amino acid sequences of IRTA1 (SEQ ID NO:32) and IRTA2 (SEQ ID NO:33) with members of the Fc Receptor family (FIG. **10**A) Multiple sequence alignment of the first two (top) and the third (bottom) extracellular Ig-domains of IRTA1 and IRTA2 to Fc receptor family members; FCGRIIA (SEQ ID NO:28), FCGRIIIA (SEQ ID NO:29), FCERIA (SEQ ID NO:30), and FCGRIA (SEQ ID NO:31). The sequences were compared using the ClustalW program (Thompson et al., 1994). Black-shaded boxes indicate conserved amino acid among all sequences; dark-grey shaded boxes indicate conserved amino acid among at least half of the sequences; light-shaded boxes indicate conservative substitutions. (FIG. **10**B) Alignment of the SH2-binding domains of IRTA1 (SEQ ID NO:35) and IRTA2 (SEQ ID NO:37) with the ITAM (SEQ ID NO:34) and ITIM (SEQ ID NO:39) consensus motifs. Conserved amino acid positions are in bold. BGP is SEQ ID NO:38 and PECAM is SEQ ID NO:36. Symbol X represents any amino acid.

FIGS. **11**A-**11**B-**4**. IRTA1 expression pattern. FIG. **11**A) Left panel. Northern blot analysis of IRTA1 mRNA expression in tissues of the human immune system. Each lane contains 2 mg mRNA. The position of RNA molecular weight markers is depicted on the right side of the blot. The positions of the IRTA1 and GAPDH mRNA transcripts are shown by arrows. (A GAPDH probe was included in the hybridization as an internal control—0.15 ng labelled+50 ng unlabelled probe—). Right Panel. Northern blot analysis of IRTA1 expression in total RNA from the ER/EB cell line (10 mg per

lane). For this experiment, cells were grown in the presence of estrogen (1 mg/ml), followed by estrogen withdrawal for the indicated times. Arrows indicate the positions of the corresponding mRNAs. a, b and c correspond to the IRTA1 differentially polyadenylated species. The same blot was stripped and reprobed with a MYC cDNA probe (exon 2) to verify cellular G_0/G_1 arrest. Densitometric analysis of IRTA1 mRNA levels is plotted in the adjacent column graph. The cDNA probe used is shown as a solid bar underneath the IRTA1 mRNA scheme in FIG. **9**A. FIG. **11**B-**1**-**11**B-4) In situ hybridization analysis of IRTA1 expression in serial sections of human tonsil. 1. Sense IRTA1 probe 2. Antisense IRTA1 probe 3. H&E staining 4. Antisense IRTA1 signal superimposed over an H&E stained section. GC, germinal center, MargZ, marginal zone

FIG. **12**A-**12**B-**4**. IRTA2 expression pattern. FIG. **12**A) Northern blot analysis of IRTA2 mRNA expression in multiple human tissues (left panel) and in various lymphoid and non-lymphoid cell lines (right panel). Each lane contains 2 mg mRNA. The positions of the IRTA2 and GAPDH transcripts are shown by arrows. a, b, c and d correspond to the alternatively spliced IRTA2 mRNA isoforms. RD, NC42 and CB33, Epstein-Barr virus transformed B lymphoblastoid cell lines; EREB, conditional EBV-transformed B lymphoblastoid cell line; FR4, plasma cell line; MOLT4 and HUT78, T cell lines; HL60 and U937, myelomonocytic cell lines; K562, erythroid cell line. The cDNA probe used is shown as a solid bar underneath the IRTA2 mRNA scheme in FIG. **9**B. FIGS. **12**B-**1**-**12**B-**4**) In situ hybridization analysis of IRTA2 mRNA expression in human tonsil. FIG. **12**B-**1**. Sense IRTA2 cDNA probe, FIG. **12**B-**2**. Antisense IRTA2 cDNA probe, FIG. **12**B-**3**. H&E staining, FIG. **12**B-**4**. Antisense IRTA2 cDNA probe signal superimposed over H&E stained section. GC, germinal center, MargZ, marginal zone

FIG. **13**. Map of the germline 1q21 region spanning the FR4 breakpoint and genomic organization of IRTA1 and IRTA2. Primers used to amplify IRTA1 exons from spleen cDNA are marked by arrowheads on top panel. Black and light boxes indicate coding and non-coding exons respectively. Arrows indicate position of BCL9, MUC1, IRTA family and FCGRIIB loci. S, SacI; H, HindIII; S, SwaI; Pc, PacI; P, PmeI; Mb, Megabases

FIGS. **14**A-**14**D. t(1;14) (q21;q32) in FR4 generates an IRTA1/Cα fusion transcript. FIG. **14**A) Schematic representation of the der(14) genomic clone lFR4B-5 and of the germline $IgC\alpha_1$ locus. The FR4 breakpoint is marked by an arrow. Filled and open boxes represent the IRTA1 and Ca_1 coding and non-coding exons respectively. FIG. **14**B) Northern blot analysis with an IRTA1 exon 1 probe (shown by a bar in FIG. **14**A) on FR4 and additional cell lines detects an abnormal message in FR4. Arrowheads point to the location of normal IRTA1 message in ER/EB mRNA. JJN3 and U266, myeloma cell lines. Two mg of polyA+ RNA loaded per lane. FIG. **14**C) Schematic representation of the IRTA1/Cα fusion cDNA in FR4. The cDNA was amplified by RT-PCR from FR4 total RNA using the primers shown in (FIG. **14**A), and sequenced after subcloning. FIG. **14**D) SDS/PAGE analysis of immunoprecipitates obtained from vector control transfected and IRTA1/Cα transient expression construct transfected 293-T cells (lanes 1 & 2), or the following cell lines: mIgA positive lymphoblastoid cell line-Dakiki (lane 3), FR4 (lane 4), mIgM positive NHL cell line-Ramos (lane 5). H, HindIII; B, BamHI; X, XhoI; Sa, IgA switch region; EC, extracellular region; TM, transmembrane; CYT, cytoplasmic

FIGS. **15**A-**15**B. IRTA2 expression is deregulated in cell lines carrying 1q21 abnormalities. FIGS. **15**A, **15**B) Northern blot analysis of IRTA2 mRNA expression in Burkitt lymphoma (FIG. **15**A) and Multiple Myeloma (FIG. **15**B) cell lines. The cDNA probe used is the same as in FIG. **12**. Each lane contains 2 mg mRNA. The positions of the IRTA2 and GAPDH mRNA transcripts are shown by dashes and arrows, respectively. The relative levels of IRTA2 mRNA expression in the left panel (FIG. **15**A) were plotted on the right panel (FIG. **15**A) after densitometric analysis and normalization versus the GAPDH levels. The right panel of (FIG. **15**B) is a summary of the Northern blot analysis results.

FIGS. **16**-**1**-**16**-**4** IRTA1 expression in normal lymphoid tissue. Paraffin-embedded sections from normal human tonsil were stained with the following antibodies: FIG. **16**-**1**) Negative control; FIG. **16**-**2**) anti-CD3 mouse monoclonal to detect T cells; FIG. **16**-**3**) anti-IRTA1 (mIRTA) mouse monoclonal; FIG. **16**-**4**) anti-IRTAL (J92884K) rabbit polyclonal. IRTA1 positive cells are located in the perifollicular and intraepithelial region of the tonsil, the equivalent of the marginal zone in the spleen.

FIG. **17** IRTA1 expression in a stomach Mucosa-Associated-Lymphoid Tissue (MALT) B cell lymphoma. A paraffin-embedded section from a stomach MALT B cell lymphoma was stained with the anti-IRTA1 (mIRTA) mouse monoclonal antibody and counterstained with H&E. The majority of MALT lymphomas analyzed were IRTA1 positive. This antibody therefore can be an effective tool in the differential diagnosis of MALT lymphoma. The mIRTA1 antibody may also be proven useful in the therapy of this B cell tumor, similarly to the use of the anti-CD20 antibody (Rituximab) in the therapy of relapsed CD20-positive lymphomas (Foon K., *Cancer J.* 6: p273).

FIG. **18**A. IRTA1 cDNA (SEQ ID NO:2) and the amino acid sequence (SEQ ID NO:1) of the encoded IRTA1 protein.

FIGS. **18**B-**1**-**18**B-**3**. IRTA2 cDNA (2a, SEQ ID NO:43; 2b, SEQ ID NO:4; 2c, SEQ ID NO:40) and the amino acid sequence (2a, SEQ ID NO:44; 2b, SEQ ID NO:3; 2c, SEQ ID NO:41) of the encoded IRTA2 protein.

FIGS. **18**C-**1**-**18**C-**2**. IRTA3 cDNA (SEQ ID NO:6) and the amino acid sequence (SEQ ID NO:5) of the encoded IRTA3 protein.

FIGS. **18**D-**1**-**18**D-**2**. IRTA4 cDNA (SEQ ID NO:8) and the amino acid sequence (SEQ ID NO:7) of the encoded IRTA4 protein.

FIGS. **18**E-**1**-**18**E-**2**. IRTA5 cDNA (SEQ ID NO:10) and the amino acid sequence (SEQ ID NO:9) of the encoded IRTA5 protein.

DETAILED DESCRIPTION OF THE INVENTION

The following standard abbreviations are used throughout the specification to indicate specific nucleotides: C=cytosine; A=adenosine; T=thymidine and G=guanosine.

This invention provides an isolated nucleic acid molecule which encodes immunoglobulin receptor, Immunoglobulin superfamily Receptor Translocation Associated, IRTA, protein.

As used herein "Immunoglobulin Receptor Translocation Associated" genes, "IRTA" are nucleic acid molecules which encode novel immunoglobulin superfamily cell surface receptors in B cells which are important in B cell development, and whose abnormal expression, e.g. deregulated expression, perturbs cell surface B cell immunological responses and thus is involved in B cell malignancy, including lymphomagenesis.

Nucleic acid molecules encoding proteins designate "MUM-2" (SEQ ID NO:15) and "MUM-3" (SEQ ID NO:17, SEQ ID NO:19 or SEQ ID NO:4) proteins in the First Series of Experiments are now called "IRTA-1" and "IRTA-2"

genes, i.e. nucleic acid molecules which encode IRTA-1 (SEQ ID NO:1) and IRTA-2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41) proteins respectively. IRTA-3 (SEQ ID NO:5), -4 (SEQ ID NO:7) and -5 (SEQ ID NO:9) proteins are members of the same the immunoglobulin gene superfamily as are the IRTA-1 and IRTA-2 proteins.

In an embodiment of the above-described isolated nucleic acid molecule which encodes immunoglobulin receptor, Immunoglobulin superfamily Receptor Translocation Associated, IRTA, protein, the encoded IRTA protein is IRTA1 protein comprising the amino acid sequence set forth in FIG. **18**A (SEQ ID NO:1).

In another embodiment of the above-described isolated nucleic acid molecule, the encoded IRTA protein is IRTA2 protein comprising the amino acid sequence set forth in FIGS. **18**B-**1**-**18**B-**3** (SEQ ID NO:44; SEQ ID NO:3; SEQ ID NO:41).

In a further embodiment of the above-described isolated nucleic acid molecule, the encoded IRTA protein is IRTA3 protein comprising the amino acid sequence set forth in FIGS. **18**C-**1**-**18**C-**2** (SEQ ID NO:5).

In yet another embodiment of the above-described isolated nucleic acid molecule, the encoded IRTA protein is IRTA4 protein comprising the amino acid sequence set forth in FIGS. **18**D-**1**-**18**D-**2** (SEQ ID NO: 7).

In a still further embodiment of the above-described isolated nucleic acid molecule, the encoded IRTA protein is IRTA5 protein comprising the amino acid sequence set forth in FIGS. **18**E-**1**-**18**E-**2** (SEQ ID NO: 9).

In another embodiment of any of the above-described isolated nucleic acid molecules, the nucleic acid molecule is DNA. In further embodiments, the DNA is cDNA. In additional embodiments, the DNA is genomic DNA. In another embodiment, the nucleic acid molecule is an RNA molecule. In yet another embodiment, the DNA molecule is cDNA having the nucleotide sequence set forth in FIG. **18**A (SEQ ID NO:2). In another embodiment, the DNA molecule is cDNA having the nucleotide sequence set forth in FIG. **18**B (SEQ ID NO:43; SEQ ID NO:4; SEQ ID NO:40). In a further embodiment, the DNA molecule is cDNA having the nucleotide sequence set forth in FIG. **18**C (SEQ ID NO:6). In another embodiment, the DNA molecule is cDNA having the nucleotide sequence set forth in FIG. **18**D (SEQ ID NO:8). In an embodiment, the DNA molecule is cDNA having the nucleotide sequence set forth in FIG. **18**E (SEQ ID NO:10). In preferred embodiments of the isolated nucleic acid molecule, wherein the nucleic acid molecules encode human IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 protein. In additional embodiments, the nucleic acid molecules encode mammalian IRTA1 protein. The mammalian IRTA1 protein may be murine IRTA1 protein. In another preferred embodiment, the isolated nucleic acid molecules are operatively linked to a promoter of DNA transcription. In yet another preferred embodiment of the isolated nucleic acid molecule, the promoter comprises a bacterial, yeast, insect, plant or mammalian promoter.

This invention provides a vector comprising any of the above-described isolated nucleic acid molecule encoding IRTA proteins, including but not limited to mammalian IRTA proteins, of which human and murine are preferred. In an embodiment, the vector is a plasmid.

This invention provides a host cell comprising the above-described vector comprising any of the above-described isolated nucleic acid molecule encoding IRTA proteins. Preferably, the isolated nucleic acid molecules in such vectors are operatively linked to a promoter of DNA transcription. In another embodiment of the host cell, the cell is selected from a group consisting of a bacterial cell, a plant cell, and insect cell and a mammalian cell.

This invention provides a method of producing an IRTA polypeptide (protein) which comprises: (a) introducing a vector comprising an isolated nucleic acid which encodes an immunoglobulin receptor, Immunoglobulin superfamily Receptor Translocation Associated, IRTA, protein into a suitable host cell; and (b) culturing the resulting cell so as to produce the polypeptide. In further embodiments, the IRTA protein produced by the above-described method may be recovered and in a still further embodiment, may be purified either wholly or partially. In an embodiment the IRTA protein may be any of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) protein. In further embodiments, any of the IRTA proteins may be mammalian proteins. In still further embodiments, the mammalian proteins may be human or mouse IRTA proteins.

IRTA genes, nucleic acid molecules encoding IRTA proteins IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9), are useful for the production of the IRTA proteins encoded thereby. IRTA proteins are useful for production of antibodies; such antibodies are used as reagents for differential diagnosis of lymphoma subtypes in hematopathology. Antibodies directed against IRTA proteins and which bind specifically to IRTA proteins also have therapeutic uses, i.e. to specifically target tumor cells, which may be used and administered similarly to "Rituximab" (an anti-CD20 antibody), which is an antibody approved by the FDA for therapy of relapsed CD20-positive lymphomas (Foon K., *Cancer J.* 6(5):273). Anti-IRTA1, anti-IRTA2, anti-IRTA3, anti-IRTA4 and anti-IRTA5 antibodies are also useful markers for isolation of specific subsets of B cells in research studies of normal and tumor B cell biology. Moreover, anti-IRTA1, anti-IRTA2, anti-IRTA3, anti-IRTA4 and anti-IRTA5 antibodies are useful research reagents to experimentally study the biology of signaling in normal and tumor B cells.

Methods of introducing nucleic acid molecules into cells are well known to those of skill in the art. Such methods include, for example, the use of viral vectors and calcium phosphate co-precipitation. Accordingly, nucleic acid molecules encoding IRTA proteins IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) may be introduced into cells for the production of these IRTA proteins.

Numerous vectors for expressing the inventive proteins IRTA1, IRTA2, IRTA3, IRTA4, and IRTA5, may be employed. Such vectors, including plasmid vectors, cosmid vectors, bacteriophage vectors and other viruses, are well known in the art. For example, one class of vectors utilizes DNA elements which are derived from animal viruses such as bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (RSV, MMTV or MOMLV), Semliki Forest virus or SV40 virus. Additionally, cells which have stably integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow for the selection of transfected host cells. The markers may provide, for example, prototrophy to an auxotrophic host, biocide resistance or resistance to heavy metals such as copper. The selectable marker gene can be either directly linked to the DNA sequences to be expressed, or introduced into the same cell by cotransformation.

Regulatory elements required for expression include promoter sequences to bind RNA polymerase and transcription initiation sequences for ribosome binding. Additional elements may also be needed for optimal synthesis of mRNA. These additional elements may include splice signals, as well as enhancers and termination signals. For example, a bacterial expression vector includes a promoter such as the lac promoter and for transcription initiation the Shine-Dalgarno sequence and the start codon AUG. Similarly, a eukaryotic expression vector includes a heterologous or homologous promoter for RNA polymerase II, a downstream polyadenylation signal, the start codon AUG, and a termination codon for detachment of the ribosome. Such vectors may be obtained commercially or assembled from the sequences described by methods well known in the art, for example the methods described above for constructing vectors in general.

These vectors may be introduced into a suitable host cell to form a host vector system for producing the inventive proteins. Methods of making host vector systems are well known to those skilled in the art.

Suitable host cells include, but are not limited to, bacterial cells (including gram positive cells), yeast cells, fungal cells, insect cells and animal cells. Suitable animal cells include, but are not limited to HeLa cells, Cos cells, CV1 cells and various primary mammalian cells. Numerous mammalian cells may be used as hosts, including, but not limited to, the mouse fibroblast cell NIH-3T3 cells, CHO cells, HeLa cells, Ltk^- cells and COS cells. Mammalian cells may be transfected by methods well known in the art such as calcium phosphate precipitation, electroporation and microinjection.

This invention provides an isolated nucleic acid molecule comprising at least 15 contiguous nucleotides capable of specifically hybridizing with a unique sequence included within the sequence of the isolated nucleic acid molecule encoding IRTA protein. In an embodiment, the IRTA protein may be IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 protein, or fragment(s) thereof, having the amino acid sequence set forth in any of FIGS. **18**A (SEQ ID NO:1), **18**B-**1**-**18**B-**3** (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), **18**C-**1**-**18**C-**2** (SEQ ID NO:5), **18**D-**1**-**18**D-**2** (SEQ ID NO:7) or **18**E-**1**-**18**E-**2** (SEQ ID NO:9), respectively. In other embodiments, the isolated nucleic acid molecules are labeled with a detectable marker. In still other embodiments of the isolated nucleic acid molecules, the detectable marker is selected from the group consisting of a radioactive isotope, enzyme, dye, biotin, a fluorescent label or a chemiluminescent label.

This invention provides a method for detecting a B cell malignancy or a type of B cell malignancy in a sample from a subject wherein the B cell malignancy comprises a 1q21 chromosomal rearrangement which comprises: a) obtaining RNA from the sample from the subject; b) contacting the RNA of step (a) with a nucleic acid molecule of at least 15 contiguous nucleotides capable of specifically hybridizing with a unique sequence included within the sequence of an isolated RNA encoding human IRTA protein selected from the group consisting of human IRTA1, IRTA2, IRTA3, IRTA4 and IRTA5, under conditions permitting hybridization of the RNA of step (a) with the nucleic acid molecule capable of specifically hybridizing with a unique sequence included within the sequence of an isolated RNA encoding human IRTA protein, wherein the nucleic acid molecule is labeled with a detectable marker; and c) detecting any hybridization in step (b), wherein detection of hybridization indicates presence of B cell malignancy or a type of B cell malignancy in the sample.

Detection of hybridization of RNA encoding IRTA proteins will indicate that a malignancy is a B cell malignancy. More specifically, detection of hybridization of RNA encoding ITRA1 protein indicates that the B cell malignancy is a Mucosa-Associated-Lymphoid Tissue (MALT) B cell lymphoma. Detection of hybridization of RNA encoding ITRA4 and IRTA5 proteins indicate that the B cell malignancy is a mantle cell lymphoma. In an embodiment of the above-described method, the B cell malignancy comprises a 1q21 chromosomal rearrangement. One of skill will use the above-described method as a diagnostic aid in conjunction with other standard methods of detecting/diagnosing malignancies, e.g. pathology of a tumor sample, which may indicate lymphoma and the above-described method will then narrow the malignancy to a B cell lymphoma or more specifically to MALT) B cell lymphoma or a mantle cell lymphoma as discussed supra.

One of skill is familiar with known methods of detecting of hybridization nucleic acid molecules to nucleic acid oligonucleotides, i.e. nucleic acid probes encoding a protein of interest for diagnostic methods. The nucleic acid molecules encoding the IRTA proteins of the subject invention are useful for detecting B cell malignancy. One of skill will recognize that variations of the above-described method for detecting a B cell malignancy in a sample include, but are not limited to, digesting nucleic acid from the sample with restriction enzymes and separating the nucleic acid molecule fragments so obtained by size fractionation before hybridization.

In an embodiment of the above-described method for detecting a B cell malignancy in a sample from a subject, wherein the detectable marker is radioactive isotope, enzyme, dye, biotin, a fluorescent label or a chemiluminescent label. In a preferred embodiment, the B cell malignancy is selected from the group consisting of B cell lymphoma, multiple myeloma, Burkitt's lymphoma, marginal zone lymphoma, diffuse large cell lymphoma and follicular lymphoma cells. In a further embodiment, the B cell lymphoma is Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT). In another preferred embodiment, the B cell lymphoma is non-Hodgkin's lymphoma.

This invention provides an antisense oligonucleotide having a sequence capable of specifically hybridizing to an mRNA molecule encoding a human ITRA protein so as to prevent overexpression of the mRNA molecule.

In preferred embodiments of the antisense oligonucleotide, the IRTA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) protein. In further embodiments of any of the above-described oligonucleotides of nucleic acid molecules encoding the IRTA1, IRTA2, IRTA3, IRTA4 and/or IRTA5 proteins, the nucleic acid may be genomic DNA or cDNA.

One of skill is familiar with conventional techniques for nucleic acid hybridization of oligonucleotides, e.g. Ausubel, F. M. et al. *Current Protocols in Molecular Biology*, (John Wiley & Sons, New York, 1998), for example stringent conditions of 65° C. in the presence of an elevated salt concentration. Such conditions are used for completely complementary nucleic acid hybridization, whereas conditions that are not stringent are used for hybridization of nucleic acids which are not totally complementary.

As used herein, the phrase "specifically hybridizing" means the ability of a nucleic acid molecule to recognize a nucleic acid sequence complementary to its own and to form double-helical segments through hydrogen bonding between complementary base pairs. As used herein, a "unique sequence" is a sequence specific to only the nucleic acid molecules encoding the IRTA1 (SEQ ID NO:1), IRTA2 (SEQ

ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) proteins. Nucleic acid probe technology is well known to those skilled in the art who will readily appreciate that such probes may vary greatly in length and may be labeled with a detectable label, such as a radioisotope or fluorescent dye, to facilitate detection of the probe. Detection of nucleic acid molecules encoding the IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) proteins is useful as a diagnostic test for any disease process in which levels of expression of the corresponding IRTA1, IRTA2, IRTA3, IRTA4 and/or IRTA5 proteins is altered. DNA probe molecules are produced by insertion of a DNA molecule which encodes mammalian IRTA1, IRTA2, IRTA3, IRTA4 and/or IRTA5 proteins or fragments thereof into suitable vectors, such as plasmids or bacteriophages, followed by insertion into suitable bacterial host cells and replication and harvesting of the DNA probes, all using methods well known in the art. For example, the DNA may be extracted from a cell lysate using phenol and ethanol, digested with restriction enzymes corresponding to the insertion sites of the DNA into the vector (discussed herein), electrophoresed, and cut out of the resulting gel. The oligonucleotide probes are useful for 'in situ' hybridization or in order to locate tissues which express this IRTA gene family, and for other hybridization assays for the presence of these genes (nucleic acid molecules encoding any of the IRTA1-IRTA5 proteins) or their mRNA in various biological tissues. In addition, synthesized oligonucleotides (produced by a DNA synthesizer) complementary to the sequence of a DNA molecule which encodes an IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) or IRTA5 (SEQ ID NO:9) protein are useful as probes for these genes, for their associated mRNA, or for the isolation of related genes by homology screening of genomic or cDNA libraries, or by the use of amplification techniques such as the Polymerase Chain Reaction.

This invention provides a purified IRTA1 protein comprising the amino acid sequence set forth in FIG. **18**A (SEQ ID NO:1). In an embodiment of the purified IRTA1 protein, wherein the IRTA1 protein is human IRTA1.

This invention provides a purified IRTA2 protein comprising the amino acid sequence set forth in FIGS. **18**B-**1**-**18**B-**3** (SEQ ID NO:44; SEQ ID NO:3; SEQ ID NO:41). In an embodiment of the purified IRTA2 protein, the IRTA2 protein is human IRTA2.

This invention provides a purified IRTA3 protein comprising the amino acid sequence set forth in FIGS. **18**C-**1**-**18**C-**2** (SEQ ID NO:5). In an embodiment of the purified IRTA3 protein, the IRTA3 protein is human IRTA3.

This invention provides a purified IRTA4 protein comprising the amino acid sequence set forth in FIGS. **18**D-**1**-**18**D-**2** (SEQ ID NO: 7). In an embodiment of the purified IRTA3 protein, wherein the IRTA4 protein is human IRTA4.

This invention provides a purified IRTA5 protein comprising the amino acid sequence set forth in FIGS. **18**E-**1**-**18**E-**2** (SEQ ID NO: 9). In an embodiment of the purified IRTA5 protein, the IRTA5 protein is human IRTA5.

In order to facilitate an understanding of the Experimental Details section which follows, certain frequently occurring methods and/or terms are best described in Sambrook, et al. (1989) and Harlow & Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, N.Y.: 1988.

This invention provides an antibody/antibodies directed to an epitope of a purified IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 protein, or fragment(s) thereof, having the amino acid sequence set forth in any of FIG. **18**A, **18**B-**1**-**18**B-**3**, **18**C-**1**-**18**C-**2**, **18**D-**1**-**18**D-**2** or **18**E-**1**-**18**E-**2**.

As used herein, the term "antibody" includes, but is not limited to, both naturally occurring and non-naturally occurring antibodies. Specifically, the term "antibody" includes polyclonal and monoclonal antibodies, and binding fragments thereof. Furthermore, the term "antibody" includes chimeric antibodies and wholly synthetic antibodies, and fragments thereof. The polyclonal and monoclonal antibodies may be "purified" which means the polyclonal and monoclonal antibodies are free of any other antibodies. As used herein, partially purified antibody means an antibody composition which comprises antibodies which specifically bind to any of the IRTA protein(s) of the subject invention, and consists of fewer protein impurities than does the serum from which the antibodies are derived. A protein impurity is a protein other than the antibodies specific for the IRTA protein(s) of the subject invention. For example, the partially purified antibodies may be an IgG preparation.

Polyclonal antibodies (anti-IRTA antibodies) may be produced by injecting a host animal such as rabbit, rat, goat, mouse or other animal with the immunogen(s) of this invention, e.g. a purified human IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5, described infra. The sera are extracted from the host animal and are screened to obtain polyclonal antibodies which are specific to the immunogen. Methods of screening for polyclonal antibodies are well known to those of ordinary skill in the art such as those disclosed in Harlow & Lane, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratories, Cold Spring Harbor, N.Y.: 1988) the contents of which are hereby incorporated by reference.

The anti-IRTA monoclonal antibodies of the subject invention may be produced by immunizing for example, mice with an immunogen (the IRTA polypeptides or fragments thereof as described herein). The mice are inoculated intraperitoneally with an immunogenic amount of the above-described immunogen and then boosted with similar amounts of the immunogen. Spleens are collected from the immunized mice a few days after the final boost and a cell suspension is prepared from the spleens for use in the fusion.

Hybridomas may be prepared from the splenocytes and a murine tumor partner using the general somatic cell hybridization technique of Kohler, B. and Milstein, C., Nature (1975) 256: 495-497. Available murine myeloma lines, such as those from the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Va. 20110-2209, USA, may be used in the hybridization. Basically, the technique involves fusing the tumor cells and splenocytes using a fusogen such as polyethylene glycol. After the fusion the cells are separated from the fusion medium and grown in a selective growth medium, such as HAT medium, to eliminate unhybridized parent cells. The hybridomas may be expanded, if desired, and supernatants may be assayed by conventional immunoassay procedures, for example radioimmunoassay, using the immunizing agent as antigen. Positive clones may be characterized further to determine whether they meet the criteria of the invention antibodies.

Hybridomas that produce such antibodies may be grown in vitro or in vivo using known procedures. The monoclonal antibodies may be isolated from the culture media or body fluids, as the case may be, by conventional immunoglobulin purification procedures such as ammonium sulfate precipitation, gel electrophoresis, dialysis, chromatography, and ultrafiltration, if desired.

In the practice of the subject invention any of the above-described antibodies may be labeled with a detectable marker.

In one embodiment, the labeled antibody is a purified labeled antibody. The term "antibody" includes, by way of example, both naturally occurring and non-naturally occurring antibodies. Specifically, the term "antibody" includes polyclonal and monoclonal antibodies, and fragments thereof. Furthermore, the term "antibody" includes chimeric antibodies and wholly synthetic antibodies, and fragments thereof. A "detectable moiety" which functions as detectable labels are well known to those of ordinary skill in the art and include, but are not limited to, a fluorescent label, a radioactive atom, a paramagnetic ion, biotin, a chemiluminescent label or a label which may be detected through a secondary enzymatic or binding step. The secondary enzymatic or binding step may comprise the use of digoxigenin, alkaline phosphatase, horseradish peroxidase, β-galactosidase, fluorescein or steptavidin/biotin. Methods of labeling antibodies are well known in the art.

Methods of recovering serum from a subject are well known to those skilled in the art. Methods of partially purifying antibodies are also well known to those skilled in the art, and include, by way of example, filtration, ion exchange chromatography, and precipitation.

The polyclonal and monoclonal antibodies of the invention may be labeled with a detectable marker. In one embodiment, the labeled antibody is a purified labeled antibody. The detectable marker may be, for example, a radioactive or fluorescent marker. Methods of labeling antibodies are well known in the art.

Determining whether the polyclonal and monoclonal antibodies of the subject invention bind to cells, e.g. cancer cells, expressing an IRTA protein and form a complex with one or more of the IRTA protein(s) described herein, or fragments thereof, on the surface of said cells, may be accomplished according to methods well known to those skilled in the art. In the preferred embodiment, the determining is accomplished according to flow cytometry methods.

The antibodies of the subject invention may be bound to an insoluble matrix such as that used in affinity chromatography. Cells which form a complex, i.e. bind, with the immobilized polyclonal or monoclonal antibody may be isolated by standard methods well known to those skilled in the art. For example, isolation may comprise affinity chromatography using immobilized antibody.

Alternatively, the antibody may be a free antibody. In this case, isolation may comprise cell sorting using free, labeled primary or secondary antibodies. Such cell sorting methods are standard and are well known to those skilled in the art.

This invention provides an antibody directed to a purified IRTA protein selected from the group consisting of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5. (SEQ ID NO:9). In a preferred embodiment of the anti-IRTA antibody the IRTA protein is human IRTA protein. The IRTA protein may be any mammalian IRTA protein, including a murine IRTA protein. In a further embodiment of any the above-described antibodies, the antibody is a monoclonal antibody. In another embodiment, the monoclonal antibody is a murine monoclonal antibody or a humanized monoclonal antibody. As used herein, "humanized" means an antibody having characteristics of a human antibody, such antibody being non-naturally occurring, but created using hybridoma techniques wherein the antibody is of human origin except for the antigen determinant portion, which is murine. In yet another embodiment, the antibody is a polyclonal antibody.

In preferred embodiments, any of the antibodies of the subject invention may be conjugated to a therapeutic agent. In further preferred embodiments, the therapeutic agent is a radioisotope, toxin, toxoid, or chemotherapeutic agent. The conjugated antibodies of the subject invention may be administered to a subject having a B cell cancer in any of the methods provided below.

This invention provides a pharmaceutical composition comprising an amount of the antibody directed to an IRTA protein effective to bind to cancer cells expressing an IRTA protein selected from the group consisting of human IRTA1, IRTA2, IRTA3, IRTA4 and IRTA5 so as to prevent growth of the cancer cells and a pharmaceutically acceptable carrier. The anti-IRTA antibody may be directed to an epitope of an IRTA protein selected from the group consisting of IRTA1, IRTA2, IRTA3, IRTA4 and IRTA5. The IRTA proteins may be human or mouse IRTA proteins.

In preferred embodiments of the above-described pharmaceutical composition, the cancer cells are selected from the group consisting of B cell lymphoma, multiple myeloma, a mantle cell lymphoma, Burkitt's lymphoma, marginal zone lymphoma, diffuse large cell lymphoma and follicular lymphoma cells. In another preferred embodiment of the pharmaceutical composition, the B cell lymphoma cells are Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT) cells. In another preferred embodiment of the pharmaceutical composition, the B cell lymphoma cells are non-Hodgkin's lymphoma cells.

This invention provides a pharmaceutical composition comprising an amount of the antibody directed to an IRTA protein effective to bind to cancer cells expressing an IRTA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) so as to prevent growth of the cancer cells and a pharmaceutically acceptable carrier. The anti-IRTA antibody may be directed to an epitope of an IRTA protein selected from the group consisting of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9). The IRTA proteins may be human or mouse IRTA proteins.

As used herein, "malignant" means capable of metastasizing. As used herein, "tumor cells" are cells which originate from a tumor, i.e., from a new growth of different or abnormal tissue. The tumor cells and cancer cells may exist as part of the tumor mass, or may exist as free-floating cells detached from the tumor mass from which they originate.

As used herein, malignant cells include, but are in no way limited to, B cell lymphoma, multiple myeloma, Burkitt's lymphoma, mantle cell lymphoma, marginal zone lymphoma, diffuse large cell lymphoma and follicular lymphoma. The B cell lymphoma is Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT) or is non-Hodgkin's lymphoma.

As used herein, "subject" is any animal or artificially modified animal. Artificially modified animals include, but are not limited to, SCID mice with human immune systems. In a preferred embodiment, the subject is a human.

This invention provides a method of diagnosing B cell malignancy which comprises a 1q21 chromosomal rearrangement in a sample from a subject which comprises: a) obtaining the sample from the subject; b) contacting the sample of step (a) with an antibody directed to a purified IRTA protein capable of specifically binding with a human IRTA protein selected from the group consisting of human IRTA1, IRTA2, IRTA3, IRTA4 and IRTA5 IRTA protein on a cell surface of a cancer cell under conditions permitting binding of the antibody with human IRTA protein on the cell surface

of the cancer cell, wherein the antibody is labeled with a detectable marker; and c) detecting any binding in step (b), wherein detection of binding indicates a diagnosis of B cell malignancy in the sample.

In an embodiment of the above-described method of diagnosing B cell malignancy, the IRTA protein is selected from the group consisting of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9). In another embodiment of the method the IRTA protein is human or mouse IRTA protein. In a further embodiment IRTA protein is purified. In a preferred embodiment of this method, the B cell malignancy is selected from the group consisting of B cell lymphoma, multiple myeloma, Burkitt's lymphoma, marginal zone lymphoma, diffuse large cell lymphoma and follicular lymphoma. In yet another embodiment of this method, the B cell lymphoma is Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT). In another preferred embodiment of this method, the B cell lymphoma is non-Hodgkin's lymphoma.

This invention provides a method of detecting human IRTA protein in a sample which comprises: a) contacting the sample with any of any of the above-described anti-IRTA antibodies under conditions permitting the formation of a complex between the antibody and the IRTA in the sample; and b) detecting the complex formed in step (a), thereby detecting the presence of human IRTA in the sample. In an embodiment the IRTA protein detected may be an IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 protein, having an amino acid sequence set forth in any of FIGS. **18**A (SEQ ID NO:1), **18**B-**1**-**18**B-**3** (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), **18**C-**1**-**18**C-**2** (SEQ ID NO:5), **18**D-**1**-**18**D-**2** (SEQ ID NO:7) or **18**E-**1**-**18**E-**2** (SEQ ID NO:9). As described hereinabove detection of the complex formed may be achieved by using antibody labeled with a detectable marker and determining presence of labeled complex. Detecting human IRTA protein in a sample from a subject is another method of diagnosing B cell malignancy in a subject. In an embodiment of this method of diagnosis, the B cell malignancy is selected from the group consisting of B cell lymphoma, multiple myeloma, Burkitt's lymphoma, marginal zone lymphoma, diffuse large cell lymphoma and follicular lymphoma. In yet another embodiment of this method, the B cell lymphoma is Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT). In another preferred embodiment of this method, the B cell lymphoma is non-Hodgkin's lymphoma.

This invention provides a method of treating a subject having a B cell cancer which comprises administering to the subject an amount of anti-IRTA antibody effective to bind to cancer cells expressing an IRTA protein so as to prevent growth of the cancer cells and a pharmaceutically acceptable carrier, thereby treating the subject. Growth and proliferation of the cancer cells is thereby inhibited and the cancer cells die. In an embodiment of the above-described method, the IRTA protein is selected from the group consisting of human IRTA1, IRTA2, IRTA3, IRTA4 and IRTA5. In a preferred embodiment of the above-described method of treating a subject having a B cell cancer, the anti-IRTA antibody is a monoclonal antibody. In another embodiment of the method, the monoclonal antibody is a murine monoclonal antibody or a humanized monoclonal antibody. The antibody may be a chimeric antibody. In a further embodiment, the anti-IRTA antibody is a polyoclonal antibody. In an embodiment, the polyclonal antibody may be a murine or human polyclonal antibody. In a preferred embodiment, the B cell cancer is selected from the group consisting of B cell lymphoma, multiple myeloma, Burkitt's lymphoma, mantle cell lymphoma marginal zone lymphoma, diffuse large cell lymphoma and follicular lymphoma. In another preferred embodiment, the B cell lymphoma is Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT). In a further preferred embodiment, the B cell lymphoma is non-Hodgkin's lymphoma. In a preferred embodiment of the above-described method of treating a subject having a B cell cancer, administration of the amount of anti-IRTA antibody effective to bind to cancer cells expressing an IRTA protein is intravenous, intraperitoneal, intrathecal, intralymphatical, intramuscular, intralesional, parenteral, epidural, subcutaneous; by infusion, liposome-mediated delivery, aerosol delivery; topical, oral, nasal, anal, ocular or optic delivery. In another preferred embodiment of the above-described methods, the anti-IRTA antibody may be conjugated to a therapeutic agent. In further preferred embodiments, the therapeutic agent is a radioisotope, toxin, toxoid, or chemotherapeutic agent.

This invention provides a method of treating a subject having a B cell cancer which comprises administering to the subject an amount of anti-IRTA antibody effective to bind to cancer cells expressing an IRTA protein so as to prevent growth of the cancer cells and a pharmaceutically acceptable carrier, thereby treating the subject. Growth and proliferation of the cancer cells is thereby inhibited and the cancer cells die. In an embodiment of the above-described method, the IRTA protein is selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9). In a preferred embodiment of the above-described method of treating a subject having a B cell cancer, the anti-IRTA antibody is a monoclonal antibody. In another embodiment of the method, the monoclonal antibody is a murine monoclonal antibody or a humanized monoclonal antibody. The antibody may be a chimeric antibody. In a further embodiment, the anti-IRTA antibody is a polyclonal antibody. In an embodiment, the polyclonal antibody may be a murine or human polyclonal antibody. In a preferred embodiment, the B cell cancer is selected from the group consisting of B cell lymphoma, multiple myeloma, Burkitt's lymphoma, mantle cell lymphoma marginal zone lymphoma, diffuse large cell lymphoma and follicular lymphoma. In another preferred embodiment, the B cell lymphoma is Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT). In a further preferred embodiment, the B cell lymphoma is non-Hodgkin's lymphoma. In a preferred embodiment of the above-described method of treating a subject having a B cell cancer, administration of the amount of anti-IRTA antibody effective to bind to cancer cells expressing an IRTA protein is intravenous, intraperitoneal, intrathecal, intralymphatical, intramuscular, intralesional, parenteral, epidural, subcutaneous; by infusion, liposome-mediated delivery, aerosol delivery; topical, oral, nasal, anal, ocular or otic delivery. In another preferred embodiment of the above-described methods, the anti-IRTA antibody may be conjugated to a therapeutic agent. In further preferred embodiments, the therapeutic agent is a radioisotope, toxin, toxoid, or chemotherapeutic agent.

The invention also provides a pharmaceutical composition comprising either an effective amount of the oligonucleotides or of the antibodies described above and a pharmaceutically acceptable carrier. In the subject invention an "effective amount" is any amount of an oligonucleotide or an antibody which, when administered to a subject suffering from a disease or abnormality against which the oligonucleotide or antibody are effective, causes reduction, remission, or regression of the disease or abnormality. In the practice of this

invention the "pharmaceutically acceptable carrier" is any physiological carrier known to those of ordinary skill in the art useful in formulating pharmaceutical compositions.

Pharmaceutically acceptable carriers are well known to those skilled in the art and include, but are not limited to, 0.01-0.1M and preferably 0.05M phosphate buffer or 0.8% saline. Additionally, such pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, antimicrobials, antioxidants, chelating agents, inert gases and the like.

In one preferred embodiment the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another equally preferred embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellent.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.

The pharmaceutical composition comprising the oligonucleotide or the antibody can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents, for example, enough saline or glucose to make the solution isotonic, bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

The pharmaceutical composition comprising the oligonucleotide or the antibody can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition or abnormality. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

EXPERIMENTAL DETAILS

First Series of Experiments

Molecular analysis of chromosomal translocations associated with multiple myeloma (MM) has indicated that the pathogenesis of this malignancy may be heterogeneous, being associated with several distinct oncogenes including BCL-1, MUM-1 and FGFR3. Structural abnormalities of chromosome 1q21, including translocations with chromosome 14q32, represent frequent cytogenetic aberrations associated with multiple myeloma. In order to identify the genes involved in these translocations, the breakpoint regions corresponding to both derivatives of a t(1;14) (q21;q32) detectable in the FR4 human plasmacytoma cell line were cloned. Analysis of the breakpoint sequences showed that they involved a reciprocal recombination between the Immunoglobulin heavy chain (IgH) locus on 14q32 and unknown sequences on 1q21. The normal locus corresponding to the 1q21 region involved in the translocation was cloned and the genes adjacent to the breakpoint region were identified by an exon-trapping strategy. Two genes were found, located within a 20 Kb distance from each other, in the region spanning the breakpoint on 1q21. The first gene, called MUM-2 (multiple myeloma-2) is expressed as a 2.5 Kb mRNA transcript detectable in spleen and lymph nodes. Cloning and sequencing of

the full-length MUM-2cDNA predicts a 515 amino acid cell surface glycoprotein containing four extracellular Ig-type domains, a transmembrane and a cytoplasmic domain and sharing a 37% identity (51% homology) with Fc gamma receptor I over its first three extracellular domains. In FR4 cells, the translocation breakpoints interrupt the MUM-2 coding domain and juxtapose it to the IgH locus in the same transcriptional orientation. As a consequence, structurally abnormal FR4-specific MUM-2 transcripts (3.0, 5.2 and 6.0 Kb) in lymph nodes and spleen and encodes a protein with an extracellular domain containing six Ig-type domains homologous to members of the Fc gamma and Ig-type adhesion receptor families. The structure of the MUM-2 and MUM-3 genes and their direct involvement in a MM-associated translocation suggest that these genes code for novel cell surface receptors important for normal lymphocyte function and B cell malignancy.

Second Series of Experiments

Experimental Procedures

Cell Lines

The MM cell lines used in this study (FR4, U266, JJN3, EJM, SKMM1, RPMI-8226, XG1, XG2, XG4, XG6, XG7) have been previously reported (Tagawa et al., 1990), (Jernberg et al., 1987), (Hamilton et al., 1990; Jackson et. al., 1989), (Eton et al., 1989), (Zhang et al., 1994). The FR4 cell line was established in the laboratory of one of the authors (S.T). The U266, JJN3, and EJM cell lines were gifts from Dr. K. Nilsson (University of Uppsala, Uppsala, Sweden) and the SKMM-1 cell line was a gift of A. N. Houghton (Memorial Sloan Kettering Cancer Center, New York, N.Y.). The five XG cell lines were obtained from Dr. Bernard Klein and cultured in the presence of 1 ng/ml human recombinant IL-6 as described previously (Zhang et al., 1994). The BL cell lines with 1q21 abnormalities have been previously described (Polito et al., 1995), (Magrath et al., 1980) and were grown in RPMI, 10% FCS.

Genomic and cDNA Library Screening and DNA Sequence Analysis

Two genomic libraries were constructed from FR4 genomic DNA either by BamHI complete digestion or by Sau3AI partial digestion and subsequent ligation of gel-purified fractions into the lDASH-II phage vector (Stratagene). The BamHI library was screened with a 4.2 kb XhoI-BamHI probe derived from the Ca locus and the Sau3AI library was screened with a 5'Sa probe previously described (Bergsagel et al., 1996). A human placental DNA library (Stratagene) was screened with probe 1.0EH (FIGS. **8**A-**8**C) to obtain the germline 1q21 locus. Library screening and plaque isolation were preformed according to established procedures (Sambrook et al., 1989). (MUM-2) and (MUM-3) cDNA clones were isolated from an oligo-dT/random-primed cDNA library constructed from normal human spleen RNA (Clontech). The IRTA1 cDNA probe used for library screening was obtained from RT-PCR of human spleen cDNA using primers flanking exons 1 and 3. DNA sequencing was preformed on an ABI 373 automated sequencer (Applied Biosystems). Sequence homology searches were carried out through the BLAST e-mail server at the National Center for Biotechnology Information, Bethesda, Md.

PAC and YAC Isolation and Exon Trapping

Human PAC clones were obtained by screening a human PAC library spotted onto nylon membranes (Research Genetics) with the 1.0 EH probe (FIGS. **8**A-**8**C). The Zeneca (formerly ICI) human YAC library (Anand et al., 1990) obtained from the United Kingdom Human Genome Mapping Resource Center (UK-HGMP) was screened using a PCR-based pooling strategy. Exon trapping was performed using the exon trapping system (Gibco BRL), according to the manufacturer's instructions.

Isolation of PAC/YAC End Clones, Pulsed-Field Gel Electrophoresis (PFGE) and Fluorescence In Situ Hybridization (FISH) Analysis

PAC DNA extraction was performed according to standard alkaline lysis methods (Drakopoli N et al., 1996). A vectorette-PCR method was used to isolate PAC and YAC end probes (Riley et al., 1990), as previously described (Iida et al, 1996). PFGE analysis was performed according to standard protocols (Drakopoli N et al., 1996) using the CHEF Mapper system (BioRad, Hercules, Calif.). Biotin labeling of PAC DNA, chromosome preparation and FISH were performed as previously described (Rao et al., 1993).

Southern and Northern blot Analyses, RACE and RT-PCR

Southern and northern blot analyses were performed as described previously (Neri et al, 1991). For Northern blot analyses total RNA was prepared by the guanidium thiocyanate method and poly(A) RNA was selected using poly(T)-coated beads (Oligotex Kit by Quigen). For Northern blots, 2 mg of poly(A) RNA were loaded per lane. Multiple tissue Northern filters were obtained from Clontech. RACE was performed using the Marathon cDNA Amplification kit (Clontech) and Marathon-Ready spleen cDNA. First strand cDNA synthesis was performed using the Superscript RT-PCR system (Gibco BRL)

In Situ Hybridization

Digoxigenin-containing antisense and sense cRNA probes were transcribed with T3 and T7 RNA polymerase, respectively, from linearized pBluescript KS+ plasmids containing coding region of cDNAs, nucleotides 62 to 1681 of IRTA1 (SEQ ID NO:1) and 18 to 2996 of IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41). Hyperplastic human tonsillar tissue surgically resected from children in Babies' Hospital, Columbia Presbyterian Medical Center was snap frozen in powdered dry ice. Cryostat sections were stored for several days at −80 degrees C. prior to processing. Non-radioactive in situ hybridization was performed essentially as described (Frank et al., 1999), except that fixation time in 4% paraformaldehyde was increased to 20 minutes, and proteinase K treatment was omitted. The stringency of hybridization was 68 degrees C., in 5×SSC, 50% formamide. Alkaline phosphatase-conjugated anti-digoxigenin antibody staining was developed with BCIP/NBT substrate.

Transfection, immunoprecipitation and Western Blotting

293 cells (ATCC), grown in DMEM, 10% FCS were transiently transfected, according to the standard calcium phosphate method, with pMT2T and pMT2T-IRTA1/Ca transient expression constructs. The latter was generated using the IRTA1/Ca RT-PCR product from FR4. Cells (2×10^6 of transfectants and 2×10^7 of remaining cell lines) were solubilized in Triton X-100 lysis buffer (150 mM NaCl, 10 mM Tris-HCl [pH 7.4], 1% Tx-100, 0.1% BSA) in the presence of a protease inhibitors cocktail (Roche Biochemicals). Lysates were incubated at 4° C. for 2 hours with 4 mg/ml of the monoclonal antibody #117-332-1 (Yu et al., 1990) (Tanox Biosystems, Inc, Houston, Tex.) that was raised against the extracellular portion of the IgA membrane peptide. Immune complexes were isolated with protein G-Sepharose (Pharmacia) prior to electrophoresis on 10-20' Tris-HCl gradient gels (Biorad) and

immunobloting, using 15 mg/ml of the #117-332-1 antibody. Results were visualized by ECL (Amersham).

Results

Molecular Cloning of the t(1;14)(q21;q32)

Chromosomal translocations involving the Ig heavy-chain (IGH) locus often occur within or near IgH switch regions as a result of "illegitimate" switch recombination events (Dalla-Favera et al., 1983; Chesi et al., 1996; Chesi et al., 1998). The breakpoints can be detected by Southern-blot hybridization assays as rearranged alleles in which the IGH constant (C_H) region sequences have lost their syntenic association with IGH joining (J_H) and 5' switch region (S) sequences (Dalla-Favera et al., 1983; Neri et al., 1988; Neri et al., 1991; Bergsagel et al., 1996). This assay has led to the identification of several chromosomal partners for the IgH locus in B-NHL and MM (Taub et al., 1982; Dalla-Favera et al., 1983; Neri et al., 1988; Neri et al., 1991; Ye et al., 1993; Chesi et al., 1996; Richelda et al., 1997; Iida et al., 1997; Dyomin et al., 1997; Dyomin et al., 2000). We employed the same strategy in order to clone the 1q21 breakpoint region in FR4, a myeloma cell line carrying a t(1;14) (q21;q32), as determined by cytogenetic analysis (Tagawa et al., 1990; Taniwaki M, unpublished results). Two "illegitimately" rearranged fragments were identified within the Cα heavy-chain locus in FR4 by Southern blot hybridization analysis (data not shown), and were cloned from phage libraries constructed from FR4 genomic DNA. Restriction mapping, Southern blot hybridization and partial nucleotide sequencing of two genomic phages (clones λ FR4B-5 and λ FR4S-a, FIG. **8**A) demonstrated that they contained the chromosomal breakpoints of a reciprocal balanced translocation between the $C\alpha_1$ locus on 14q32 and non-IGH sequences. A probe (1.0EH) representing these non-IgH sequences (FIG. **8**A) was then used to clone the corresponding normal genomic locus from phage, P1 artificial chromosome (PAC), and yeast artificial chromosome (YAC) human genomic libraries. Fluorescence in situ hybridization (FISH) analysis of normal human metaphase spreads using the 100-kb non-chimaeric PAC clone 49A16 which spans the breakpoint region (see below, FIG. **13**), identified the partner chromosomal locus as derived from band 1q21 (FIG. **8**C). Mapping to a single locus within chromosome 1 was confirmed by hybridization of two non-repetitive probes to DNA from a somatic-cell hybrid panel representative of individual human chromosomes (data not shown). These results were consistent with the cloning of sequences spanning the t(1;14) (q21;q32) in FR4.

Sequence analysis of the breakpoint regions on the derivative chromosomes and alignment with the germline 14q32 and 1q21 loci (SEQ ID NO:24 and SEQ ID NO:26, respectively) revealed that the breakpoint had occurred in the intron between the CH3 and the transmembrane exon of $C\alpha_1$ on chromosome 14. Although the breakpoint region was devoid of recombination signal sequences (RSS) or switch signal sequences (Kuppers et al., 1999), the sequence CTTAAC (underlined on FIG. **8**B) was present in both germline chromosomes 14 and 1 at the breakpoint junction (SEQ ID NO:25 and SEQ ID NO:27, respectively). One copy of this sequence was present in each of the derivative chromosomes, with a slight modification in the der(1) copy (point mutation in the last nucleotide: C to G). The nucleotides AT preceding CTTAAC on chromosome 1 were also present in both derivative chromosomes (FIG. **8**B). The translocation did not result in any loss of chromosome 1 sequences. On the other hand, in the chromosome 14 portion of der(1) we observed two deletions upstream of the breakpoint junction: a 16 nucleotide deletion (GGCACCTCCCCTTAAC) (SEQ ID NO:42) and a 4 nucleotide deletion (TGCA) 6 nucleotides upstream (FIG. **8**B). These observations indicate that the t(1;14)(q21;q32) in FR4 cells represents a balanced reciprocal translocation possibly facilitated by the presence of homologous sequences (CTTAAC) on both chromosomes.

The 1q21 Breakpoint Region Contains Genes Coding for Novel Members of the Immunoglobulin Receptor Superfamily

We next investigated whether the region of chromosome 1q21 spanning the translocation breakpoint in FR4 contains a transcriptional unit. DNA from partially overlapping PAC clones 49A16 and 210K22 (FIG. **13**) was "shotgun" cloned in plasmids, sequenced and analyzed for homology to known genes in human genome databases. In parallel, candidate genes on the 49A16 PAC were sought by an exon trapping strategy (Church et al., 1994).

Mapping of the candidate exons on the 1q21 genomic clones revealed that the FR4 breakpoint had occurred between two trapped exons (see below, FIG. **13**), which belonged to the same transcript since they could be linked by RT-PCR using spleen RNA. This RT-PCR product was then used as a probe to screen a spleen cDNA library in order to isolate full-length clones corresponding to this transcript. Two sets of cDNA clones were identified, belonging to two distinct transcripts and sharing a 76% mRNA sequence identity within the 443 bp probe region. Full length cDNA clones for both transcripts were obtained by rapid amplification of cDNA ends (RACE) on human spleen cDNA that generated 5' and 3' extension products.

The schematic structure of the cDNA representing the first transcript is depicted in FIG. **9**A. Alternate usage of three potential polyadenylation sites in its 3' untranslated region gives rise to three mRNA species of 2.6, 2.7 and 3.5 kb, encoding the same putative 515-amino acid protein (FIG. **9**A). The predicted features of this protein include a signal peptide, in accordance with the [−3, −1] rule (von Heijne, 1986), four extracellular Ig-type domains carrying three potential asparagine (N)-linked glycosylation sites (FIG. **9**A), a 16 amino acid transmembrane and a 106 amino acid cytoplasmic domain with three putative consensus Src-homology 2 (SH2)-binding domains (Unkeless and Jin, 1997) (FIG. **10**B). These (SH2)-binding domains exhibit features of both ITAM (Immune-receptor Tyrosine-based Activation Motif—$D/EX_7D/EX_2YXXL/IX_{6-8}YXXL/I$; where X denotes non-conserved residues) (Reth, 1989) and ITIM motifs (Immune-receptor lyrosine-based Inhibition Motif—S/V/L/IYXXL/V where X denotes non-conserved residues) (Unkeless and Jin, 1997). As shown in FIG. **10**B, the first two SH2-binding domains are spaced 8 aminoacids apart, consistent with the consensus ITAM motif. Diverging from the consensus, the glutamate residue (E) is positioned four rather than two aminoacids before the first tyrosine (Y) (FIG. **10**B), and the +3 position relative to tyrosine (Y) is occupied by valine (V) rather than leucine (L) or isoleucine (I) (Cambier, 1995). All three domains conform to the ITIM consensus and each is encoded by a separate exon, as is the case for ITIM. Thus their arrangement may give rise to three ITIM or possibly to one ITAM and one ITIM. The overall structure of this protein suggests that it represents a novel transmembrane receptor of the Ig superfamily and it was therefore name IRTA1 (Immune Receptor Translocation Associated gene 1).

The second cDNA shares homology to IRTA1 (68% nucleotide identity for the length of the IRTA1 message encoding its extracellular domain) and was named IRTA2. The IRTA2 locus is more complex than IRTA1 and is transcribed into three major mRNA isoforms (IRTA2a, IRTA2b, IRTA2c) of

different molecular weight (2.8, 4.7 and 5.4 kb respectively), each with its own unique 3' untranslated region (FIG. **9**B). In addition, a 0.6 kb transcript (FIG. **12**A) arises from the usage of an early polyadenylation signal at nucleotide 536 of IRTA2. The three predicted IRTA2 protein isoforms encoded by these transcripts share a common aminoacid sequence until residue 560, featuring a common signal peptide and six extracellular Ig-type domains (FIG. **9**B). IRTA2a encodes for a 759 aa secreted glycoprotein with eight Ig-type domains followed by 13 unique, predominantly polar aminoacids at its C-terminus. IRTA2b diverges from IRTA2a at amino acid residue 560, and extends for a short stretch of 32 additional residues, whose hydrophobicity is compatible with its docking to the plasma membrane via a GPI-anchor (Ferguson and Williams, 1988). IRTA2c is the longest isoform whose sequence deviates from IRTA2a at aminoacid 746. It encodes a 977 aa type I transmembrane glycoprotein with nine extracellular Ig-type domains, harboring eight potential N-linked glycosylation sites, a 23 aminoacid transmembrane and a 104 aminoacid cytoplasmic domain with three consensus SH2-binding motifs (FIG. **10**B). Each of the SH2-binding sites in IRTA2c agrees with the ITIM consensus (FIG. **10**B) and is encoded by a separate exon. These features suggest that IRTA2c is a novel transmembrane receptor of the Ig superfamily with secreted and GPI-linked isoforms.

Homology Between the IRTA Proteins and Immunoglobulin Superfamily Receptors

Amino acid alignment of the entire extracellular domains of the IRTA1 and IRTA2 proteins to each other and to other Ig superfamily members revealed a remarkable homology between them (47% identity and 51% similarity) and a lower, but striking homology to the Fc gamma receptor family of proteins. This homology was stronger in the aminoacid positions conserved among the different classes of Fc receptors. Among Fc receptors, the high affinity IgG receptor FCGR1 (CD64) shared the highest levels of homology with the first three Ig-domains of IRTA1 and IRTA2 (37% identity and 50% similarity) throughout its entire extracellular portion (FIG. **10**A). Lower levels of homology were observed between the IRTA proteins and the extracellular domains of other cell surface molecules, including human platelet endothelial cell adhesion molecule (PECAM1), B-lymphocyte cell adhesion molecule (CD22) and Biliary Glycoprotein 1 (BGP1) (22-25% identity, 38-41% homology).

No homology is apparent between the IRTAs and members of the Fc receptor family in their cytoplasmic domains. In contrast, significant aminoacid homology is present between IRTA1 and PECAM1 (31% aminoacid identity and 45% homology), IRTA2c and BGP1 (30% identity, 35% homology) and IRTA2c and PECAM1 (28% identity, 50% homology) (FIG. **10**B). These homologies suggest employment of similar downstream signaling pathways by these different proteins.

IRTA1 and IRTA2 are Normally Expressed in Specific Subpopulations of B Cells

The normal expression pattern of the IRTA1 and IRTA2 mRNAs was first analyzed by Northern blot hybridization of RNA derived from different normal human tissues and from human cell lines representing different hematopoietic lineages and stages of B-cell development.

IRTA1 expression was detected at a very low level in human spleen and lymph node RNA (FIG. **11**A, left panel) and was undetectable in all other human tissues analyzed, including fetal liver, bone marrow, lung, placenta, small intestine, kidney, liver, colon, skeletal muscle, heart and brain (data not shown). Among B cell lines, IRTA1 expression was absent in cell lines representing pre-B and germinal center B-cells, plasma cells and cells of erythroid, T-cell and myeloid origin (data not shown, see Materials and Methods). Expression was detectable at very low levels only in EBV-immortalized lymphoblastoid cell lines (LCL), which represent a subpopulation (immunoblasts) positioned downstream of germinal center B cells in B-cell differentiation. However, expression was induced in estrogen-deprived ER/EB cells which, being immortalized by a recombinant EBV genome in which the EBNA2 gene is fused to the estrogen receptor, proliferate in the presence of estrogen while they arrest in the G_0/G_1 phase upon estrogen deprivation (Kempkes et al., 1995). IRTA1 expression was barely detectable in these cells in the presence of estrogen, but was induced (10-fold) upon their G_0/G_1 arrest following estrogen withdrawal (FIG. **11**A, right panel). Taken together, these results suggest that IRTA1 is expressed in a lymphoid subpopulation present in spleen and lymph nodes and presumably represented by resting B cells.

To further investigate the phenotype and tissue distribution of the cells expressing IRTA1, we performed in situ hybridization on human tonsillar tissue using a IRTA1 antisense cDNA probe (FIG. **11**B). Serial sections were processed for in situ hybridization with a control sense cDNA probe (Panel #**1** in FIG. **11**B), an antisense cDNA probe (Panel #**2**) and hematoxylin and eosin (H&E) staining (Panel #**3**) to outline the architecture of the lymphoid tissue. The IRTA1 hybridization signal was excluded from the germinal center and the mantle zone of the follicles and was characteristically concentrated in the perifollicular zone with infiltrations in the intra-epithelial region (FIGS. **11**B-**2**, **11**B-**4**). In this region, only B cells were positive as documented by staining with B cell specific markers (IgD, not shown), and by immunohistochemical analysis with anti-IRTA1 and anti-B (CD20, PAX5), anti-T (CD3), and anti-monocyte (CD68) antibodies (not shown; G. Cattoretti et al., manuscript in preparation). This perifollicular area is the "marginal zone" equivalent of the tonsil, representing a functionally distinct B-cell compartment that contains mostly memory B-cells and monocytoid B-cells (de Wolf-Peeters et al., 1997). Together with the Northern blot analysis of normal tissues and cell lines, these results indicate that IRTA1 is expressed in a subpopulation of resting mature B-cells topographically located in the perifollicular and intraepithelial region, sites rich in memory B cells.

In the case of IRTA2, Northern blot analysis detected all alternatively spliced species in human lymph node, spleen, bone marrow and small intestine mRNA, with relative preponderance of the IRTA2a isoform (FIG. **12**A, left panel). Among the hematopoietic cell lines of lymphoid and non-lymphoid origin tested, IRTA2 expression was restricted to B-cell lines with an immunoblastic, post-germinal center phenotype (FIG. **12**A, right panel). Similarly to IRTA1, it was absent from cell lines derived from pre-B cells, germinal center centroblasts, plasma cells, T-cells, erythroid cells and myeloid cells (FIG. **12**A, right panel).

In situ hybridization analysis of human tonsillar tissue, using the IRTA2c cDNA as a probe, was consistent with the results of the Northern blot analysis. The IRTA2 mRNA was largely excluded from the mantle zone of the germinal center, with the exception of a few positive cells (FIGS. **12**B-**2**, **12**B**4**). Within the germinal center, the dark zone, represented by centroblasts, appeared negative for IRTA2, while the light zone, rich in centrocytes, was strongly positive (FIGS. **12**B-**2**, **12**B-**4**). Finally, IRTA2 mRNA was detected in the "marginal zone" equivalent region outside germinal center follicles and in the intraepithelial and interfollicular regions of the tonsil.

This pattern is consistent with specificity of IRTA2 for centrocytes and post-germinal center B cells. Comparing their expression patterns, we conclude that both are specific for mature B cells, but IRTA2 has a broader pattern of expression that includes centrocytes and interfollicular B cells, while IRTA1 is restricted to marginal zone B cells, most likely memory cells.

Genomic Organization of the IRTA1 and IRTA2 Genes

To understand the consequences of 1q21 abnormalities on IRTA1 and IRTA2 gene structure and expression, we first determined the organization of their genomic loci. The IRTA1 gene contains 11 exons with a total genomic size of 24.5 kb (FIG. **13**). The IRTA2 locus was found to span a genomic region of approximately 40 kb (FIG. **13**). The three IRTA2 alternatively spliced products share their first 8 exons, at which point IRTA2b does not utilize the next splicing site, and terminates by entering its 3'UTR region. IRTA2a and 2c isoforms splice into exon 9, with IRTA2a entering into its 3'UTR after exon 11 and IRTA2c splicing into exon 12 and extending until exon 18 (FIG. **13**).

Based on sequencing data, we determined that the IRTA1 and IRTA2 genes are located 21 kb distant from each other, juxtaposed in the same transcriptional orientation (FIG. **13**) that extends from the telomere (5') towards the centromere (3'). At the 1q21 locus, they are tightly linked to each other as well as to three additional genes we recently cloned through their homology to the IRTAs (I.M, manuscript in preparation). All five genes are contiguous, covering a ~300 kb region at 1q21. This region is located at the interval between previously reported 1q21 breakpoints. Based on the distance between genomic clones harboring the respective genes on the Whitehead Institute Radiation Hybrid map, the IRTA1-2 locus is estimated to lie approximately 0.8 Mb away from the MUC1 locus towards the telomere (N.P, unpublished data; Dyomin et al., 2000; Gilles et al., 2000) and less than or equal to 7 Mb away from the FCGRIIB locus towards the centromere (N.P, unpublished data).

The t(1;14) (q21;q32) Translocation Generates an IRTA1/Ca_1 Fusion Protein in the FR4 Myeloma Cell Line

Comparative restriction and nucleotide sequence analysis of germline versus rearranged sequences from the Ca_1 and IRTA1 loci showed that the translocation had fused sequences within intron 2 of the IRTA1 gene to the intronic sequences between the CH3 and the transmembrane exon of Ca_1 in the same transcriptional orientation (FIG. **14**A). This suggested that, if IRTA1 sequences were expressed in the translocated locus, the intact donor site at the 3' border of the IRTA1 exon and the intact acceptor site at the 5' of Ca_1 could be used to generate a fusion IRTA1/Ca_1 mRNA, and possibly a IRTA1/Ca_1 fusion protein.

In order to test this prediction, we analyzed IRTA1 mRNA expression in FR4 by Northern blot analysis using an IRTA1 cDNA probe derived from exon 1 (FIG. **14**A). This probe detected a 0.8 kb message in FR4 that was absent from other B-cell lines, and was shorter than the normal 2.5 kb message detectable in ER/EB cells (FIG. **14**B). We cloned this transcript by RT-PCR of FR4 mRNA using primers derived from sequences at the 5' border of IRTA1 exon 1 and the 3' border of the Cα cytoplasmic exon (FIG. **14**A). An RT-PCR product was obtained from FR4, but not from the DAKIKI cell line expressing wild-type surface IgA, or other cell lines lacking a t(1;14) translocation (data not shown). Direct sequencing analysis of the PCR product indicated that splicing had precisely linked IRTA1 and Ca_1 at canonical splicing sites and determined that the fusion transcript was 820 bp long.

Analysis of the predicted protein product indicated that the IRTA1/$C\alpha_1$ splicing had resulted in a fusion between the IRTA1 signal peptide and first two extracellular aminoacids, with the 32-amino acid long extracellular spacer, transmembrane domain and cytoplasmic tail of the membrane IgA_1 ($mIgA_1$) receptor (FIG. **14**C). To assay for the expression of this fusion protein in FR4 protein extracts, we used an antibody directed against extracellular aminoacid residues specific for the transmembrane isoform of $C\alpha_1$ (Yu et al., 1990) for immunoprecipitation, followed by Western blotting. Our results demonstrated that FR4 cells, but not a control cell line (DAKIKI) expressing wild-type surface IgA, express a 9.8 kDa protein consistent with the predicted size of IRTA1/$C\alpha_1$ fusion protein (FIG. **14**D). These results show that the translocated allele encodes a fusion protein, composed of the signal peptide and first two extracellular residues of IRTA1 (17 aminoacids) fused to the $C\alpha_1$ encoded transmembrane and cytoplasmic domains (71 aminoacids). In contrast to IRTA1/Ca_1 overexpression on der(14), no expression was detected in FR4 for the reciprocal Ca_1/IRTA1 transcript or for the intact IRTA2 gene on der(1).

With the exception of FR4, IRTA1 mRNA expression was not detected in any other myeloma or lymphoma cell line, regardless of the status of its chromosomal band 1q21 (data not shown). Thus, the IRTA1/Ca fusion represents a rare event in 1q21 aberrations.

Frequent Deregulation of IRTA2 Expression in Cell Lines Carrying 1q21 Abnormalities

In order to establish the physical relationship between other 1q21 breakpoints and the IRTA1/2 locus, we performed FISH analysis with the PAC 49A16 on our panel of BL and MM cell lines. Among ten BL cell lines analyzed, seven with dup(1)(q21q32) and three with 1q21 translocations (AS283A, BL104, BL136), we detected three signals corresponding to the IRTA1/IRTA2 locus in seven of the former and two of the latter, consistent with dup(1) (q21q32) in the first case and dup(1)(q21q32) followed by a translocation breakpoint at 1q21 in the second. (Table 1). FISH analysis of AS283A and BL136, using probes spanning the IRTA locus and with neighboring genomic clones, placed the breakpoint of the derivative chromosomes outside the IRTA locus in both cell lines, at a distance of >800 kb towards the centromere in AS283A and >800 kb towards the telomere in BL136 (N.P, unpublished results). Consistent with this finding, analysis of 30 cases of MM primary tumors by interphase FISH with the 300-kb YAC 23GC4 (FIG. **13**), showed that 15 cases (50% of total analyzed) had more than two interphase FISH signals (data not shown), while double color FISH with two PAC clones flanking the YAC centromeric and telomeric borders detected no split of these two probes in any of the cases. These results indicate that, with the exception of FR4, the breakpoints of 1q21 aberrations in BL or MM are not within or in close proximity to the genomic region defined by IRTA1 and IRTA2. However, the consistent outcome of either dup(1) (q21q32) (see Table 1) or dup(1)(q21q32) followed by unbalanced translocations (AS283A, BL136, XG2, XG7 in Table 1) is partial trisomy or tetrasomy of the region of 1q21 containing the IRTA genes.

TABLE 1

Summary of karyotypic and FISH data on IRTA1/IRTA2 locus

Tumour type	Cytogenetics	PAC 49A16	Copy number of IRTA locus by FISH	IRTA2 mRNA expression
Burkitt Lymphoma				
AS283A	der(4) t(1;4)(q21;q35)	der(4), normal 1	3	++++++
MC116	dup1q21	dup1q21	3	+++
CA46	dup1q21	dup1q21	3	+++
PA682	dup1q21	dup1q21	3	++
BrgIgA	dup1q21	dup1q21	3	++
BL32	dup1q21	dup1q21	3	–
BL92	dup1q21	dup1q21	3	++
BL103	invdup1q21	dup1q21	3	+
BL104	t(1;3)(q21;p25)	der(1)	2	+
BL136	der(1)(qpter1q21::q21)	der(1)	3	++
Multiple Myeloma				
XG2	der(1) t(1;?)(q21;?)	der(1), normal 1	3	++++
	der 19 t(1;19)(q12;?)	der(19)		
XG7	der(9) t(1;9)(q12;?)	der(9)	4	–
	der(19) t(1;19)(q12;?)	der(19)		
	der(1) t(1;?)(q21;?)×2	der(1)×2		

We then investigated whether these aberrations had an effect on IRTA2 mRNA expression. To this end, we used a cDNA probe corresponding to the IRTA2 5' untranslated region to screen a Northern blot with a panel of B-NHL and MM cell lines lacking or displaying 1q21 chromosomal abnormalities. The results show that most (ten out of twelve) BL lines with normal 1q21 chromosomes essentially lack IRTA2 expression, consistent with the fact that BL derive from GC centroblasts which normally lack IRTA2 expression (FIG. **15**A, left panel). In contrast, most BL lines carrying 1q21 abnormalities (ten out of twelve) clearly display IRTA2 mRNA upregulation (FIG. **15**A, right panel), ranging from 2 to 50 fold over baseline levels detected in BL with normal 1q21. Among myeloma cell lines, IRTA2 was overexpressed in one out of three lines displaying 1q21 abnormalities (XG2), while it was expressed in none out of seven with normal 1q21 (FIG. **15**B).

These results show a strong correlation between the presence of 1q21 chromosomal aberrations and deregulation of IRTA2 mRNA expression in BL and suggest that trisomies of the IRTA2 locus may deregulate its expression in this lymphoma subtype (see Discussion).

Discussion

Efforts described herein to identify genes involved in chromosomal aberrations affecting band 1q21 in Multiple Myeloma and B cell lymphoma, led to the discovery of IRTA1 and IRTA2, two founding members of a novel subfamily of related receptors within the immunoreceptor family; full length nucleic acid sequences encoding IRTA1 and IRTA2 proteins are provided herein, as are the amino acid sequences of the encoded IRTA1 and IRTA2 proteins. Subsequently three additional genes of members of this subfamily of related receptors were isolated, IRTA3, IRTA4, and IRTA5, the full length nucleic acid sequences of which are provided herein, as are the amino acid sequences of the encoded IRTA3, IRTA4, and IRTA5 proteins. These results have implications for the normal biology of B cells as well as for the role of 1q21 aberrations in lymphomagenesis.

IRTA1 and IRTA2 are Founding Members of a New Subfamily within the Ig Superfamily

Several features shared between the two IRTA genes and their encoded proteins suggest that they form a new subfamily within the immunoreceptor superfamily. First, they share a higher degree of homology with each other in their extracellular domains than with other superfamily members both in their mRNA (68% identity) and protein (47% identity) sequence. Second, they share homology in their cytoplasmic domains, marked by the presence of ITAM-like and ITIM signaling motifs in the context of homologous aminoacid sequences. Third, IRTA1 and IRTA2 belong to a larger subfamily of five genes displaying higher intrafamily homology and tight clustering within a ~300 kb region at 1q21 (I. M. et al., manuscript in preparation). Their genomic organization suggests that a common ancestral gene may have given rise to this subfamily, by a process of duplication and sequence divergence, similar to the mechanism proposed for the Fc receptor family (Qiu et al., 1990).

In their extracellular domain, the IRTA proteins are closely related to the Fc receptor subfamily based on the high degree of aminoacid homology shared especially with the high affinity FCGR1 receptor (37-45% aminoacid identity). A common evolutionary origin with Fc receptors is also suggested by the position of the IRTA family locus in the interval between the FCGR1 locus on 1q21 and the FCERI and FCGRII-III loci on 1q21-q23. Finally, the IRTA and FCR genes share a similar exon/intron organization of the gene portion that encodes their signal peptide, in particular the two 5' leader exons with the sequences encoding the signal peptidase site located within the second 21-bp exon.

Based on their cytoplasmic ITIM-like motifs, the IRTA proteins can be considered members of the Inhibitory Receptor Superfamily (IRS), a group of receptors that block activation of many cell types in the immune system (Lanier, 1998). Such members include FCGRIIB and CD22 in the human (DeLisser et al., 1994) and PIR-B in the mouse (Kubagawa et al., 1997). Analogous to IRS members, the ITIM of IRTA1 and IRTA2 are encoded by individual exons. A feature that many IRS members share is the existence of corresponding activating receptor isoforms whose cytoplasmic domains are devoid of ITIM (reviewed in Ravetch and Lanier, 1998). It is possible that the secreted isoform of IRTA2, which lacks ITIM-like motifs, fulfills an analogous role by counteracting the effect of the transmembrane isoform.

Significant homology in the sequence and overall organization of their extracellular portion is shared among the IRTA1 and IRTA2 proteins and the Cell Adhesion Molecule (CAM) subfamily members PECAM1, CD22 and BGP1. In addition, the ability of IRTA2 to generate three protein isoforms with distinct subcellular localization (a transmembrane, a GPI-linked or a secreted protein) by differential splicing is shared by NCAM, another member of the CAM subfamily (Dickson et al., 1987; Gower et al., 1988). Thus, the IRTA family is also related to the CAM family, as has been previously suggested for a member of the Fc receptor family (murine FCGR11) because of its homology to PECAM1 (CAM, IRS family) (Daeron, 1991; Newman et al., 1990; Stockinger et al., 1990).

In conclusion, the IRTA family may represent an intersection among the Fc, IRS and CAM families, combining features from all three. Accordingly, IRTA proteins may have a role in the regulation of signal transduction during an immune response (like Fc receptors), intercellular communication (like members of the IRS and CAM families) and cell migration (like CAM family members) (DeLisser et al., 1994; Ravetch and Lanier, 2000). Initial experiments indicate that

IRTA1 can weakly bind heat aggregated IgA, while IRTA2c can specifically bind heat aggregated human serum IgG (with higher affinity for IgG_1 and IgG_2), but not monomeric human IgG, IgA, IgM and IgE (data not shown). These initial data lend support to a functional relationship between the IRTA and the Fc receptor families, but do not exclude functions dependent on other ligands for the IRTA proteins.

Differential Pattern of Expression of IRTA Genes in Mature B Cells

The IRTA genes display a specific pattern of expression in various normal B cell compartments. IRTA1 is topographically restricted to B cells within the perifollicular region, which was originally named marginal zone in the spleen, but is also detectable in most lymphoid organs (de Wolf-Peeters et al., 1997). The in situ hybridization data presented here have been confirmed by immunohistochemical analysis using anti-IRTA1 antibodies which show that the IRTA1 protein is selectively expressed in marginal zone B cells, and, among NHL, in marginal zone lymphoma, the tumors deriving from these cells (G. Cattoretti et al., manuscript in preparation). On the other hand, IRTA2 has a broader pattern of expression that includes GC centrocytes, as well as a broad spectrum of perifollicular cells, which may include immunoblasts and memory cells. Initial data suggest that the pattern of expression of IRTA3 is analogous to IRTA2, while IRTA4 and IRTA5 are selectively expressed in mantle zone B cells (I. Miller et al., manuscript in preparation), the pre-GC compartment of mature B cells (MacLennan, I. C., 1994). This topographic restriction of IRTA gene expression in lymphoid organs suggests that the IRTA molecules may play a role in the migration or activity of various B cell subpopulations in specific functional B cell compartments. In addition, IRTA expression should be useful for the differential diagnosis of NHL subtypes deriving from various B cell compartments, particularly IRTA1 in the diagnosis of marginal zone lymphoma.

IRTA1 Locus and 1q21 Abnormalities in MM

In the FR4 cell line, the consequence of the t(1;14) translocation is the formation of an IRTA1/$C\alpha_1$ fusion gene. Despite the fact that this gene is driven by the IRTA1 promoter region, which is normally silent in plasma cells, its expression is high in FR4, presumably due to the influence of the $C\alpha_1$ 3' LCR, which is retained downstream of the $C\alpha_1$ locus. The fusion gene encodes a IRTA1/$C\alpha_1$ fusion protein which contains only the signal peptide and first two amino acids of IRTA1 linked to the surface IgA receptor. The latter has been almost completely deprived of its extracellular domain, but retains all its transmembrane and intracellular domains. This structure indicates that the IRTA1/$C\alpha_1$ fusion protein, though probably unable to bind any ligand, may retain the potential for dimerization and signaling. In particular, the membrane (m) IgA-derived extracellular portion contains a cysteine residue, which can be involved in disulphide bonds between two α-chains or between a-chains and associated proteins, such as the auxilliary surface receptor CD19 (Leduc et al., 1997). The fusion protein also carries the intact, 14 amino acid mIgA cytoplasmic domain, which is highly conserved in evolution (Reth, 1992) and may play an essential role in the proliferation, survival and differentiation of mature B-cells, analogous to the role of mIgG and mIgE (Kaisho et al., 1997). Thus, the emergence of the IRTA1/Ca_1 protein in FR4 may have provided the cells with a proliferative and survival advantage during tumor development through ligand (antigen)-independent activation of the BCR pathway. This fusion event however, appears to be rare in B-cell malignancy, since so far we were able to detect it only in FR4 cells.

IRTA2 Locus and 1q21 Abnormalities in MM and BL

Abnormal expression of IRTA2 is a frequent consequence of 1q21 abnormalities. Although this gene is not expressed normally either in centroblasts, the presumed normal counterparts of BL (Kuppers et al., 1999), or in BL with normal 1q21, its levels are upregulated on average by 10-fold in BL cell lines with 1q21 abnormalities. This deregulation appears to be specific for IRTA2 since all the other 4 IRTA genes present within 300 kb on 1q21 are either not expressed in BL (IRTA1), or their pattern of expression does not correlate with the presence of 1q21 abnormalities (IRTA3, 4, 5, not shown). The mechanism by which this deregulation occurs is difficult to ascertain in the absence of structural lesions within or adjacent to the IRTA2 gene. Since the heterogeneous aberrations that affect 1q21 all cause an excess copy number of the IRTA locus, it is possible that this may lead to regulatory disturbances, as is the case for low level amplification of BCL2 in FL lacking (14;18) translocations (Monni et al., 1997), REL in diffuse large cell lymphoma (Houldsworth et al., 1996; Rao et al., 1998) and deregulation of Cyclin D1 in some MM cases with trisomy 11 (Pruneri et al., 2000). On the other hand, 1q21 abnormalities, including translocations and duplications, change the genomic context of the IRTA locus and may lead to deregulation of IRTA2 by distant cis-acting enhancer chromatin organizing elements acting on its promoter as is the case for MYC in endemic BL (Pelicci et al., 1986) and MM (Shou et al., 2000) and for CCND1 in mantle cell lymphoma (Bosch et al., 1994; Swerdlow et al., 1995) and MM (Pruneri et al., 2000).

The biological consequences of deregulated IRTA2 expression are difficult to predict at this stage. The observation that IRTA2 has homology with CAM adhesion receptors, together with its specific distribution in the light zone of the GC suggest that its ectopic expression in centroblasts may cause a disruption in the GC development and architecture. On the other hand, our initial observations that IRTA2 can bind IgG immune complexes comparably to bona fide Fc receptors suggest that its inappropriate expression may perturb the dynamics of cell surface regulation of B cell immunological responses, possibly leading to clonal expansion. Deregulated expression of FCGR2B as a result of the t(1;14)(q21;q32) in follicular lymphoma has been proposed to contribute to lymphomagenesis in this tumor type (Callanan et al., 2000), by a mechanism involving escape by tumor cells of anti-tumor immune surveillance through their Fc binding and inactivation of tumor specific IgG. Similar evasion mechanisms have been observed in cells infected by Fc-encoding herpesvisures (Dubin et al., 1991). The role of IRTA2 deregulation needs to be tested in "gain of function" transgenic mice constitutively expressing IRTA2 in the GC.

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Zhang, X. G., Gaillard, J. P., Robillard, N., Lu, Z. Y., Gu, Z. J., Jourdan, M., Boiron, J. M., Bataille, R., and Klein, B. (1994). Reproducible obtaining of human myeloma cell lines as a model for tumor stem cell study in human multiple myeloma. Blood 83, 3654-63.

Third Series of Experiments

Chromosome 1q21 is frequently altered by translocations and duplications in several types of B cell malignancy, including multiple myeloma, Burkitt lymphoma, marginal zone lymphomas, and follicular lymphoma. To identify the genes involved in these aberrations, cloned was the chromosomal breakpoint of a t(11;14)(q21;q32) in the myeloma cell line FR4. A 300 kb region spanning the breakpoint contains at least five highly related adjacent genes which encode surface receptor molecules that are members of the immunoglobulin gene superfamily, and thus called IRTA (Immunoglobulin Receptor Translocation Associated). The various IRTA molecules have from three to nine extracellular immunoglobulin superfamily domains and are related to the Fc gamma receptors. They have transmembrane and cytoplasmic domains containing ITIM-like and ITAM-like (ITRA-1, IRTA-3, IRTA-4) signaling motifs. In situ hybridization experiments show that all IRTA genes are expressed in the B cell lineage with distinct developmental stage-specific patterns: IRTA-1 is expressed in a marginal B cell pattern. IRTA-2 is expressed in centrocytes and more mature B cells. As a result of the translocation in FR4, IRTA-1 is broken and produces a fusion transcript with the immunoglobulin locus. The IRTA-2 gene, normally silent in centroblasts, is overexpressed in multiple myeloma and in Burkitt lymphoma cell lines carrying 1q21 abnormalities. The data here suggests that IRTA genes are novel B cell regulatory molecules that may also have a role in lymphomagenesis.

SEQUENCE LISTING

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Thr Phe Phe Lys Gly Glu Arg Val Thr Leu Thr Cys Asn Gly Phe Gln
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Phe Tyr Ala Thr Glu Lys Thr Thr Trp Tyr His Arg His Tyr Trp Gly
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Glu Lys Leu Thr Leu Thr Pro Gly Asn Thr Leu Glu Val Arg Glu Ser
65                  70                  75                  80

Gly Leu Tyr Arg Cys Gln Ala Arg Gly Ser Pro Arg Ser Asn Pro Val
                85                  90                  95

Arg Leu Leu Phe Ser Ser Asp Ser Leu Ile Leu Gln Ala Pro Tyr Ser
            100                 105                 110

Val Phe Glu Gly Asp Thr Leu Val Leu Arg Cys His Arg Arg Arg Lys
        115                 120                 125

Glu Lys Leu Thr Ala Val Lys Tyr Thr Trp Asn Gly Asn Ile Leu Ser
    130                 135                 140

Ile Ser Asn Lys Ser Trp Asp Leu Leu Ile Pro Gln Ala Ser Ser Asn
145                 150                 155                 160

Asn Asn Gly Asn Tyr Arg Cys Ile Gly Tyr Gly Asp Glu Asn Asp Val
                165                 170                 175

Phe Arg Ser Asn Phe Lys Ile Ile Lys Ile Gln Glu Leu Phe Pro His
            180                 185                 190

Pro Glu Leu Lys Ala Thr Asp Ser Gln Pro Thr Glu Gly Asn Ser Val
        195                 200                 205

Asn Leu Ser Cys Glu Thr Gln Leu Pro Pro Glu Arg Ser Asp Thr Pro
    210                 215                 220

Leu His Phe Asn Phe Phe Arg Asp Gly Glu Val Ile Leu Ser Asp Trp
225                 230                 235                 240

Ser Thr Tyr Pro Glu Leu Gln Leu Pro Thr Val Trp Arg Glu Asn Ser
                245                 250                 255

Gly Ser Tyr Trp Cys Gly Ala Glu Thr Val Arg Gly Asn Ile His Lys
            260                 265                 270

His Ser Pro Ser Leu Gln Ile His Val Gln Arg Ile Pro Val Ser Gly
        275                 280                 285

Val Leu Leu Glu Thr Gln Pro Ser Gly Gly Gln Ala Val Glu Gly Glu
    290                 295                 300

Met Leu Val Leu Val Cys Ser Val Ala Glu Gly Thr Gly Asp Thr Thr
305                 310                 315                 320

Phe Ser Trp His Arg Glu Asp Met Gln Glu Ser Leu Gly Arg Lys Thr
                325                 330                 335

Gln Arg Ser Leu Arg Ala Glu Leu Glu Leu Pro Ala Ile Arg Gln Ser
            340                 345                 350

His Ala Gly Gly Tyr Tyr Cys Thr Ala Asp Asn Ser Tyr Gly Pro Val
        355                 360                 365

Gln Ser Met Val Leu Asn Val Thr Val Arg Glu Thr Pro Gly Asn Arg
    370                 375                 380

Asp Gly Leu Val Ala Ala Gly Ala Thr Gly Gly Leu Leu Ser Ala Leu
385                 390                 395                 400

Ile Leu Ala Val Ala Leu Leu Phe His Cys Trp Arg Arg Arg Lys Ser
                405                 410                 415

Gly Val Gly Phe Leu Gly Asp Glu Thr Arg Leu Pro Pro Ala Pro Gly
            420                 425                 430

Pro Gly Glu Ser Ser His Ser Ile Cys Pro Ala Gln Val Glu Leu Gln
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Ser Leu Tyr Val Asp Val His Pro Lys Lys Gly Asp Leu Val Tyr Ser
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Glu Ile Gln Thr Thr Gln Leu Gly Glu Glu Glu Glu Ala Asn Thr Ser
465                 470                 475                 480

Arg Thr Leu Leu Glu Asp Lys Asp Val Ser Val Val Tyr Ser Glu Val
                485                 490                 495

Lys Thr Gln His Pro Asp Asn Ser Ala Gly Lys Ile Ser Ser Lys Asp
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Glu Glu Ser
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<212> TYPE: DNA
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<400> SEQUENCE: 2

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cgaggttcgg gaatctggac tgtacagatg ccaggcccgg ggctccccac gaagtaaccc    420

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gggatactac tgtacagcag acaacagcta cggccctgtc cagagcatgg tgctgaatgt   1260

cactgtgaga gagaccccag gcaacagaga tggccttgtc gccgcgggag ccactggagg   1320

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gataaagaga gagaaggact gttatgaaaa acagaagcac aaattttggt gaattgggat   2040

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            20                  25                  30

Thr Val Phe Gln Gly Glu Arg Val Thr Leu Thr Cys Lys Gly Phe Arg
        35                  40                  45

Phe Tyr Ser Pro Gln Lys Thr Lys Trp Tyr His Arg Tyr Leu Gly Lys
    50                  55                  60

Glu Ile Leu Arg Glu Thr Pro Asp Asn Ile Leu Glu Val Gln Glu Ser
65                  70                  75                  80

Gly Glu Tyr Arg Cys Gln Ala Gln Gly Ser Pro Leu Ser Ser Pro Val
                85                  90                  95

His Leu Asp Phe Ser Ser Ala Ser Leu Ile Leu Gln Ala Pro Leu Ser
            100                 105                 110

Val Phe Glu Gly Asp Ser Val Val Leu Arg Cys Arg Ala Lys Ala Glu
        115                 120                 125

Val Thr Leu Asn Asn Thr Ile Tyr Lys Asn Asp Asn Val Leu Ala Phe
    130                 135                 140

Leu Asn Lys Arg Thr Asp Phe His Ile Pro His Ala Cys Leu Lys Asp
145                 150                 155                 160

Asn Gly Ala Tyr Arg Cys Thr Gly Tyr Lys Glu Ser Cys Cys Pro Val
                165                 170                 175

Ser Ser Asn Thr Val Lys Ile Gln Val Gln Glu Pro Phe Thr Arg Pro
            180                 185                 190

Val Leu Arg Ala Ser Ser Phe Gln Pro Ile Ser Gly Asn Pro Val Thr
        195                 200                 205

Leu Thr Cys Glu Thr Gln Leu Ser Leu Glu Arg Ser Asp Val Pro Leu
    210                 215                 220

Arg Phe Arg Phe Phe Arg Asp Asp Gln Thr Leu Gly Leu Gly Trp Ser
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Leu Ser Pro Asn Phe Gln Ile Thr Ala Met Trp Ser Lys Asp Ser Gly
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Phe Tyr Trp Cys Lys Ala Ala Thr Met Pro His Ser Val Ile Ser Asp
            260                 265                 270

Ser Pro Arg Ser Trp Ile Gln Val Gln Ile Pro Ala Ser His Pro Val
        275                 280                 285

Leu Thr Leu Ser Pro Glu Lys Ala Leu Asn Phe Glu Gly Thr Lys Val
    290                 295                 300

Thr Leu His Cys Glu Thr Gln Glu Asp Ser Leu Arg Thr Leu Tyr Arg
305                 310                 315                 320

Phe Tyr His Glu Gly Val Pro Leu Arg His Lys Ser Val Arg Cys Glu
                325                 330                 335

Arg Gly Ala Ser Ile Ser Phe Ser Leu Thr Thr Glu Asn Ser Gly Asn
            340                 345                 350

Tyr Tyr Cys Thr Ala Asp Asn Gly Leu Gly Ala Lys Pro Ser Lys Ala
        355                 360                 365

Val Ser Leu Ser Val Thr Val Pro Val Ser His Pro Val Leu Asn Leu
    370                 375                 380

Ser Ser Pro Glu Asp Leu Ile Phe Glu Gly Ala Lys Val Thr Leu His
385                 390                 395                 400

Cys Glu Ala Gln Arg Gly Ser Leu Pro Ile Leu Tyr Gln Phe His His
                405                 410                 415

Glu Asp Ala Ala Leu Glu Arg Arg Ser Ala Asn Ser Ala Gly Gly Val
            420                 425                 430

Ala Ile Ser Phe Ser Leu Thr Ala Glu His Ser Gly Asn Tyr Tyr Cys
        435                 440                 445

Thr Ala Asp Asn Gly Phe Gly Pro Gln Arg Ser Lys Ala Val Ser Leu
    450                 455                 460

Ser Ile Thr Val Pro Val Ser His Pro Val Leu Thr Leu Ser Ser Ala
465                 470                 475                 480

Glu Ala Leu Thr Phe Glu Gly Ala Thr Val Thr Leu His Cys Glu Val
                485                 490                 495

Gln Arg Gly Ser Pro Gln Ile Leu Tyr Gln Phe Tyr His Glu Asp Met
            500                 505                 510

Pro Leu Val Ser Ser Ser Thr Pro Ser Val Gly Arg Val Ser Phe Ser
        515                 520                 525

Phe Ser Leu Thr Glu Gly His Ser Gly Asn Tyr Tyr Cys Thr Ala Asp
    530                 535                 540

Asn Gly Phe Gly Pro Gln Arg Ser Glu Val Val Ser Leu Phe Val Thr
545                 550                 555                 560

Gly Lys Cys Trp Val Leu Ala Ser Lys Pro Pro Leu Ala Glu Phe Ser
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Thr Ala Phe Lys Gly Glu Lys Val Ala Leu Ile Cys Ser Ser Ile Ser
35 40 45

His Ser Leu Ala Gln Gly Asp Thr Tyr Trp Tyr His Asp Glu Lys Leu
50 55 60

Leu Lys Ile Lys His Asp Lys Ile Gln Ile Thr Glu Pro Gly Asn Tyr
65 70 75 80

Gln Cys Lys Thr Arg Gly Ser Ser Leu Ser Asp Ala Val His Val Glu
85 90 95

Phe Ser Pro Asp Trp Leu Ile Leu Gln Ala Leu His Pro Val Phe Glu
100 105 110

Gly Asp Asn Val Ile Leu Arg Cys Gln Gly Lys Asp Asn Lys Asn Thr
115 120 125

His Gln Lys Val Tyr Tyr Lys Asp Gly Lys Gln Leu Pro Asn Ser Tyr
130 135 140

Asn Leu Glu Lys Ile Thr Val Asn Ser Val Ser Arg Asp Asn Ser Lys
145 150 155 160

Tyr His Cys Thr Ala Tyr Arg Lys Phe Tyr Ile Leu Asp Ile Glu Val
165 170 175

Thr Ser Lys Pro Leu Asn Ile Gln Val Gln Glu Leu Phe Leu His Pro
180 185 190

Val Leu Arg Ala Ser Ser Ser Thr Pro Ile Glu Gly Ser Pro Met Thr
195 200 205

Leu Thr Cys Glu Thr Gln Leu Ser Pro Gln Arg Pro Asp Val Gln Leu
210 215 220

Gln Phe Ser Leu Phe Arg Asp Ser Gln Thr Leu Gly Leu Gly Trp Ser
225 230 235 240

Arg Ser Pro Arg Leu Gln Ile Pro Ala Met Trp Thr Glu Asp Ser Gly
245 250 255

Ser Tyr Trp Cys Glu Val Glu Thr Val Thr His Ser Ile Lys Lys Arg
260 265 270

Ser Leu Arg Ser Gln Ile Arg Val Gln Arg Val Pro Val Ser Asn Val
275 280 285

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Asn Leu Glu Ile Arg Pro Thr Gly Gly Gln Leu Ile Glu Gly Glu Asn
    290                 295                 300

Met Val Leu Ile Cys Ser Val Ala Gln Gly Ser Gly Thr Val Thr Phe
305                 310                 315                 320

Ser Trp His Lys Glu Gly Arg Val Arg Ser Leu Gly Arg Lys Thr Gln
                325                 330                 335

Arg Ser Leu Leu Ala Glu Leu His Val Leu Thr Val Lys Glu Ser Asp
            340                 345                 350

Ala Gly Arg Tyr Tyr Cys Ala Ala Asp Asn Val His Ser Pro Ile Leu
        355                 360                 365

Ser Thr Trp Ile Arg Val Thr Val Arg Ile Pro Val Ser His Pro Val
    370                 375                 380

Leu Thr Phe Arg Ala Pro Arg Ala His Thr Val Val Gly Asp Leu Leu
385                 390                 395                 400

Glu Leu His Cys Glu Ser Leu Arg Gly Ser Pro Pro Ile Leu Tyr Arg
                405                 410                 415

Phe Tyr His Glu Asp Val Thr Leu Gly Asn Ser Ser Ala Pro Ser Gly
            420                 425                 430

Gly Gly Ala Ser Phe Asn Leu Ser Leu Thr Ala Glu His Ser Gly Asn
        435                 440                 445

Tyr Ser Cys Asp Ala Asp Asn Gly Leu Gly Ala Gln His Ser His Gly
    450                 455                 460

Val Ser Leu Arg Val Thr Val Pro Val Ser Arg Pro Val Leu Thr Leu
465                 470                 475                 480

Arg Ala Pro Gly Ala Gln Ala Val Val Gly Asp Leu Leu Glu Leu His
                485                 490                 495

Cys Glu Ser Leu Arg Gly Ser Phe Pro Ile Leu Tyr Trp Phe Tyr His
            500                 505                 510

Glu Asp Asp Thr Leu Gly Asn Ile Ser Ala His Ser Gly Gly Gly Ala
        515                 520                 525

Ser Phe Asn Leu Ser Leu Thr Thr Glu His Ser Gly Asn Tyr Ser Cys
    530                 535                 540

Glu Ala Asp Asn Gly Leu Gly Ala Gln His Ser Lys Val Val Thr Leu
545                 550                 555                 560

Asn Val Thr Gly Thr Ser Arg Asn Arg Thr Gly Leu Thr Ala Ala Gly
                565                 570                 575

Ile Thr Gly Leu Val Leu Ser Ile Leu Val Leu Ala Ala Ala Ala Ala
            580                 585                 590

Leu Leu His Tyr Ala Arg Ala Arg Arg Lys Pro Gly Gly Leu Ser Ala
        595                 600                 605

Thr Gly Thr Ser Ser His Ser Pro Ser Glu Cys Gln Glu Pro Ser Ser
    610                 615                 620

Ser Arg Pro Ser Arg Ile Asp Pro Gln Glu Pro Thr His Ser Lys Pro
625                 630                 635                 640

Leu Ala Pro Met Glu Leu Glu Pro Met Tyr Ser Asn Val Asn Pro Gly
                645                 650                 655

Asp Ser Asn Pro Ile Tyr Ser Gln Ile Trp Ser Ile Gln His Thr Lys
            660                 665                 670

Glu Asn Ser Ala Asn Cys Pro Met Met His Gln Glu His Glu Glu Leu
        675                 680                 685

Thr Val Leu Tyr Ser Glu Leu Lys Lys Thr His Pro Asp Asp Ser Ala
    690                 695                 700

Gly Glu Ala Ser Ser Arg Gly Arg Ala His Glu Glu Asp Asp Glu Glu
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705 710 715 720

Asn Tyr Glu Asn Val Pro Arg Val Leu Leu Ala Ser Asp His
725 730

<210> SEQ ID NO 6
<211> LENGTH: 2970
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

agtgaagggg tttcccatat gaaaaataca gaaagaatta tttgaatact agcaaataca 60

caacttgata tttctagaga acccaggcac agtcttggag acattactcc tgagagactg 120

cagctgatgg aagatgagcc ccaacttcta aaaatgtatc actaccggga ttgagataca 180

aacagcattt aggaaggtct catctgagta gcagcttcct gccctccttc ttggagataa 240

gtcgggcttt tggtgagaca gactttccca accctctgcc cggccggtgc ccatgcttct 300

gtggctgctg ctgctgatcc tgactcctgg aagagaacaa tcaggggtgg ccccaaaagc 360

tgtacttctc ctcaatcctc catggtccac agccttcaaa ggagaaaaag tggctctcat 420

atgcagcagc atatcacatt ccctagccca gggagacaca tattggtatc acgatgagaa 480

gttgttgaaa ataaaacatg acaagatcca aattacagag cctggaaatt accaatgtaa 540

gacccgagga tcctccctca gaattacaga gcctggaaat taccaatgta agacccgagg 600

atcctccctc agacatcctg tctttgaagg agacaatgtc attctgagat gtcaggggaa 660

agacaacaaa aacactcatc aaaaggttta ctacaaggat ggaaaacagc ttcctaatag 720

ttataattta gagaagatca cagtgaattc agtctccagg gataatagca aatatcattg 780

tactgcttat aggaagtttt acatacttga cattgaagta acttcaaaac ccctaaatat 840

ccaagttcaa gagctgtttc tacatcctgt gctgagagcc agctcttcca cgcccataga 900

ggggagtccc atgaccctga cctgtgagac ccagctctct ccacagaggc cagatgtcca 960

gctgcaattc tccctcttca gagatagcca gaccctcgga ttgggctgga gcaggtcccc 1020

cagactccag atccctgcca tgtggactga agactcaggg tcttactggt gtgaggtgga 1080

gacagtgact cacagcatca aaaaaaggag cctgagatct cagatacgtg tacagagagt 1140

ccctgtgtct aatgtgaatc tagagatccg gcccaccgga gggcagctga ttgaaggaga 1200

aaatatggtc cttatttgct cagtagccca gggttcaggg actgtcacat tctcctggca 1260

caaagaagga agagtaagaa gcctgggtag aaagacccag cgttccctgt tggcagagct 1320

gcatgttctc accgtgaagg agagtgatgc agggagatac tactgtgcag ctgataacgt 1380

tcacagcccc atcctcagca cgtggattcg agtcaccgtg agaattccgg tatctcaccc 1440

tgtcctcacc ttcagggctc ccagggccca cactgtggtg ggggacctgc tggagcttca 1500

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atgtgaggct gacaatggcc tgggggccca gcacagtaaa gtggtgacac tcaatgttac 1980

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aggaacttcc aggaacagaa caggccttac cgctgcggga atcacggggc tggtgctcag 2040

catcctcgtc cttgctgctg ctgctgctct gctgcattac gccagggccc gaaggaaacc 2100

aggaggactt tctgccactg gaacatctag tcacagtcct agtgagtgtc aggagccttc 2160

ctcgtccagg ccttccagga tagaccctca agagcccact cactctaaac cactagcccc 2220

aatggagctg gagccaatgt acagcaatgt aaatcctgga gatagcaacc cgatttattc 2280

ccagatctgg agcatccagc atacaaaaga aaactcagct aattgtccaa tgatgcatca 2340

agagcatgag gaacttacag tcctctattc agaactgaag aagacacacc cagacgactc 2400

tgcaggggag gctagcagca gaggcagggc ccatgaagaa gatgatgaag aaaactatga 2460

gaatgtacca cgtgtattac tggcctcaga ccactagccc cttacccaga gtggcccaca 2520

ggaaacagcc tgcaccattt ttttttctgt tctctccaac cacacatcat ccatctctcc 2580

agactctgcc tcctacgagg ctgggctgca gggtatgtga ggctgagcaa aaggtctgca 2640

aatctcccct gtgcctgatc tgtgtgttcc ccaggaagag agcaggcagc ctctgagcaa 2700

gcactgtgtt attttcacag tggagacacg tggcaaggca ggagggccct cagctcctag 2760

ggctgtcgaa tagaggagga gagagaaatg gtctagccag ggttacaagg gcacaatcat 2820

gaccatttga tccaagtgtg atcgaaagct gttaatgtgc tctctgtata aacaatttgc 2880

tccaaatatt ttgtttccct tttttgtgtg gctggtagtg gcattgctga tgttttggtg 2940

tatatgctgt atccttgcta ccatattggg 2970

<210> SEQ ID NO 7
<211> LENGTH: 508
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Leu Leu Trp Ser Leu Leu Val Ile Phe Asp Ala Val Thr Glu Gln
1 5 10 15

Ala Asp Ser Leu Thr Leu Val Ala Pro Ser Ser Val Phe Glu Gly Asp
20 25 30

Ser Ile Val Leu Lys Cys Gln Gly Glu Gln Asn Trp Lys Ile Gln Lys
35 40 45

Met Ala Tyr His Lys Asp Asn Lys Glu Leu Ser Val Phe Lys Lys Phe
50 55 60

Ser Asp Phe Leu Ile Gln Ser Ala Val Leu Ser Asp Ser Gly Asn Tyr
65 70 75 80

Phe Cys Ser Thr Lys Gly Gln Leu Phe Leu Trp Asp Lys Thr Ser Asn
85 90 95

Ile Val Lys Ile Lys Val Gln Glu Leu Phe Gln Arg Pro Val Leu Thr
100 105 110

Ala Ser Ser Phe Gln Pro Ile Glu Gly Gly Pro Val Ser Leu Lys Cys
115 120 125

Glu Thr Arg Leu Ser Pro Gln Arg Leu Asp Val Gln Leu Gln Phe Cys
130 135 140

Phe Phe Arg Glu Asn Gln Val Leu Gly Ser Gly Trp Ser Ser Ser Pro
145 150 155 160

Glu Leu Gln Ile Ser Ala Val Trp Ser Glu Asp Thr Gly Ser Tyr Trp
165 170 175

Cys Lys Ala Glu Thr Val Thr His Arg Ile Arg Lys Gln Ser Leu Gln
180 185 190

Ser Gln Ile His Val Gln Arg Ile Pro Ile Ser Asn Val Ser Leu Glu

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        195                 200                 205

Ile Arg Ala Pro Gly Gly Gln Val Thr Glu Gly Gln Lys Leu Ile Leu
    210                 215                 220

Leu Cys Ser Val Ala Gly Gly Thr Gly Asn Val Thr Phe Ser Trp Tyr
225                 230                 235                 240

Arg Glu Ala Thr Gly Thr Ser Met Gly Lys Lys Thr Gln Arg Ser Leu
                245                 250                 255

Ser Ala Glu Leu Glu Ile Pro Ala Val Lys Glu Ser Asp Ala Gly Lys
            260                 265                 270

Tyr Tyr Cys Arg Ala Asp Asn Gly His Val Pro Ile Gln Ser Lys Val
        275                 280                 285

Val Asn Ile Pro Val Arg Ile Pro Val Ser Arg Pro Val Leu Thr Leu
    290                 295                 300

Arg Ser Pro Gly Ala Gln Ala Ala Val Gly Asp Leu Leu Glu Leu His
305                 310                 315                 320

Cys Glu Ala Leu Arg Gly Ser Pro Pro Ile Leu Tyr Gln Phe Tyr His
                325                 330                 335

Glu Asp Val Thr Leu Gly Asn Ser Ser Ala Pro Ser Gly Gly Gly Ala
            340                 345                 350

Ser Phe Asn Leu Ser Leu Thr Ala Glu His Ser Gly Asn Tyr Ser Cys
        355                 360                 365

Glu Ala Asn Asn Gly Leu Gly Ala Gln Cys Ser Glu Ala Val Pro Val
    370                 375                 380

Ser Ile Ser Gly Pro Asp Gly Tyr Arg Arg Asp Leu Met Thr Ala Gly
385                 390                 395                 400

Val Leu Trp Gly Leu Phe Gly Val Leu Gly Phe Thr Gly Val Ala Leu
                405                 410                 415

Leu Leu Tyr Ala Leu Phe His Lys Ile Ser Gly Glu Ser Ser Ala Thr
            420                 425                 430

Asn Glu Pro Arg Gly Ala Ser Arg Pro Asn Pro Gln Glu Phe Thr Tyr
        435                 440                 445

Ser Ser Pro Thr Pro Asp Met Glu Glu Leu Gln Pro Val Tyr Val Asn
    450                 455                 460

Val Gly Ser Val Asp Val Asp Val Val Tyr Ser Gln Val Trp Ser Met
465                 470                 475                 480

Gln Gln Pro Glu Ser Ser Ala Asn Ile Arg Thr Leu Leu Glu Asn Lys
                485                 490                 495

Asp Ser Gln Val Ile Tyr Ser Ser Val Lys Lys Ser
            500                 505


<210> SEQ ID NO 8
<211> LENGTH: 2580
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

tggtgaccaa gagtacatct cttttcaaat agctggatta ggtcctcatg ctgctgtggt     60

cattgctggt catctttgat gcagtcactg aacaggcaga ttcgctgacc cttgtggcgc    120

cctcttctgt cttcgaagga gacagcatcg ttctgaaatg ccagggagaa cagaactgga    180

aaattcagaa gatggcttac ataaggata acaaagagtt atctgttttc aaaaaattct    240

cagatttcct tatccaaagt gcagttttaa gtgacagtgg taactatttc tgtagtacca    300

aaggacaact ctttctctgg gataaaactt caaatatagt aaagataaaa gtccaagagc    360
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tctttcaacg tcctgtgctg actgccagct ccttccagcc catcgaaggg ggtccagtga 420

gcctgaaatg tgagacccgg ctctctccac agaggttgga tgttcaactc cagttctgct 480

tcttcagaga aaaccaggtc ctggggtcag gctggagcag ctctccggag ctccagattt 540

ctgccgtgtg gagtgaagac acagggtctt actggtgcaa ggcagaaacg gtgactcaca 600

ggatcagaaa acagagcctc caatcccaga ttcacgtgca gagaatcccc atctctaatg 660

taagcttgga gatccgggcc cccgggggac aggtgactga aggacaaaaa ctgatcctgc 720

tctgctcagt ggctgggggt acaggaaatg tcacattctc ctggtacaga gaggccacag 780

gaaccagtat gggaaagaaa acccagcgtt ccctgtcagc agagctggag atcccagctg 840

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gaggctctcc cccaatcttg taccaatttt atcatgagga tgtcaccctt gggaacagct 1080

cggccccctc tggaggaggg gcctccttca acctctcttt gactgcagaa cattctggaa 1140

actactcctg tgaggccaac aacggcctgg gggcccagtg cagtgaggca gtgccagtct 1200

ccatctcagg acctgatggc tatagaagag acctcatgac agctggagtt ctctggggac 1260

tgtttggtgt ccttggtttc actggtgttg ctttgctgtt gtatgccttg ttccacaaga 1320

tatcaggaga aagttctgcc actaatgaac ccagaggggc ttccaggcca aatcctcaag 1380

agttcaccta ttcaagccca accccagaca tggaggagct gcagccagtg tatgtcaatg 1440

tgggctctgt agatgtggat gtggtttatt ctcaggtctg gagcatgcag cagccagaaa 1500

gctcagcaaa catcaggaca cttctggaga acaaggactc ccaagtcatc tactcttctg 1560

tgaagaaatc ataacacttg gaggaatcag aagggaagat caacagcaag gatggggcat 1620

cattaagact tgctataaaa ccttatgaaa atgcttgagg cttatcacct gccacagcca 1680

gaacgtgcct caggaggcac ctcctgtcat ttttgtcctg atgatgtttc ttctccaata 1740

tcttctttta cctatcaata ttcattgaac tgctgctaca tccagacact gtgcaaataa 1800

attatttctg ctaccttctc ttaagcaatc agtgtgtaaa gatttgaggg aagaatgaat 1860

aagagataca aggtctcacc ttcatctact gtgaagtgat gagaacagga cttgatagtg 1920

gtgtattaac ttatttatgt gctgctggat acagtttgct aatattttgt tgagaatttt 1980

tgcaaatatg ttcattggga atattggcct gaaatttttct tttccactgt gtctctgcca 2040

gaatgtttgt atcaggctga tgctggcttc atagaatgag ttaggcagga gcccttcctc 2100

cttgattttt tggcatagtt tcagcaggat tggtaccagt tattctttct gcatcttgta 2160

gaattcagct atgaatccat ctggtctagg gcttttgtgt tggttggtaa gtttttttatt 2220

actaattcaa cttcagcgct tgatattggt ctaggagggg tttctgtctc ttcctggttc 2280

aatcttggga gattgtgtgt ttccaggaat ttagccgttt cctccagatt ttcttcttta 2340

tgtgcatcga cttgagtgta aacataactt atatgcactg ggaaaccaaa aaatctgtgt 2400

gacttgcttt attgcagcat ttgttttatt ttggtagtct ggaactgaac ctgcaatatc 2460

accaaagtat gcatatagtt gcaaaaatgt gatttttgac atagtaaata tgagtatttg 2520

caataaacta tgatattact tttgtaagta tatagaataa aatgtaaata atctataaaa 2580

<210> SEQ ID NO 9
<211> LENGTH: 429
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 9

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Met Leu Pro Arg Leu Leu Leu Leu Ile Cys Ala Pro Leu Cys Glu Pro
1               5                  10                  15

Ala Glu Leu Phe Leu Ile Ala Ser Pro Ser His Pro Thr Glu Gly Ser
            20                  25                  30

Pro Val Thr Leu Thr Cys Lys Met Pro Phe Leu Gln Ser Ser Asp Ala
        35                  40                  45

Gln Phe Gln Phe Cys Phe Phe Arg Asp Thr Arg Ala Leu Gly Pro Gly
    50                  55                  60

Trp Ser Ser Ser Pro Lys Leu Gln Ile Ala Ala Met Trp Lys Glu Asp
65                  70                  75                  80

Thr Gly Ser Tyr Trp Cys Glu Ala Gln Thr Met Ala Ser Lys Val Leu
                85                  90                  95

Arg Ser Arg Arg Ser Gln Ile Asn Val His Arg Val Pro Val Ala Asp
            100                 105                 110

Val Ser Leu Glu Thr Gln Pro Pro Gly Gly Gln Val Met Glu Gly Asp
        115                 120                 125

Arg Leu Val Leu Ile Cys Ser Val Ala Met Gly Thr Gly Asp Ile Thr
    130                 135                 140

Phe Leu Trp Tyr Lys Gly Ala Val Gly Leu Asn Leu Gln Ser Lys Thr
145                 150                 155                 160

Gln Arg Ser Leu Thr Ala Glu Tyr Glu Ile Pro Ser Val Arg Glu Ser
                165                 170                 175

Asp Ala Glu Gln Tyr Tyr Cys Val Ala Glu Asn Gly Tyr Gly Pro Ser
            180                 185                 190

Pro Ser Gly Leu Val Ser Ile Thr Val Arg Ile Pro Val Ser Arg Pro
        195                 200                 205

Ile Leu Met Leu Arg Ala Pro Arg Ala Gln Ala Ala Val Glu Asp Val
    210                 215                 220

Leu Glu Leu His Cys Glu Ala Leu Arg Gly Ser Pro Pro Ile Leu Tyr
225                 230                 235                 240

Trp Phe Tyr His Glu Asp Ile Thr Leu Gly Ser Arg Ser Ala Pro Ser
                245                 250                 255

Gly Gly Gly Ala Ser Phe Asn Leu Ser Leu Thr Glu Glu His Ser Gly
            260                 265                 270

Asn Tyr Ser Cys Glu Ala Asn Asn Gly Leu Gly Ala Gln Arg Ser Glu
        275                 280                 285

Ala Val Thr Leu Asn Phe Thr Val Pro Thr Gly Ala Arg Ser Asn His
    290                 295                 300

Leu Thr Ser Gly Val Ile Glu Gly Leu Leu Ser Thr Leu Gly Pro Ala
305                 310                 315                 320

Thr Val Ala Leu Leu Phe Cys Tyr Gly Leu Lys Arg Lys Ile Gly Arg
                325                 330                 335

Arg Ser Ala Arg Asp Pro Leu Arg Ser Leu Pro Ser Pro Leu Pro Gln
            340                 345                 350

Glu Phe Thr Tyr Leu Asn Ser Pro Thr Pro Gly Gln Leu Gln Pro Ile
        355                 360                 365

Tyr Glu Asn Val Asn Val Val Ser Gly Asp Glu Val Tyr Ser Leu Ala
    370                 375                 380

Tyr Tyr Asn Gln Pro Glu Gln Glu Ser Val Ala Ala Glu Thr Leu Gly
385                 390                 395                 400

Thr His Met Glu Asp Lys Val Ser Leu Asp Ile Tyr Ser Arg Leu Arg
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405 410 415

Lys Ala Asn Ile Thr Asp Val Asp Tyr Glu Asp Ala Met
420 425

<210> SEQ ID NO 10
<211> LENGTH: 2303
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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atctgtgctc cactctgtga acctgccgag ctgtttttga tagccagccc ctcccatccc 120

acagagggga gcccagtgac cctgacgtgt aagatgccct ttctacagag ttcagatgcc 180

cagttccagt tctgcttttt cagagacacc cgggccttgg gcccaggctg gagcagctcc 240

cccaagctcc agatcgctgc catgtggaaa gaagacacag ggtcatactg gtgcgaggca 300

cagacaatgg cgtccaaagt cttgaggagc aggagatccc agataaatgt gcacagggtc 360

cctgtcgctg atgtgagctt ggagactcag cccccaggag gacaggtgat ggagggagac 420

aggctggtcc tcatctgctc agttgctatg ggcacaggag acatcacctt cctttggtac 480

aaaggggctg taggtttaaa ccttcagtca aagacccagc gttcactgac agcagagtat 540

gagattcctt cagtgaggga gagtgatgct gagcaatatt actgtgtagc tgaaaatggc 600

tatggtccca gccccagtgg gctggtgagc atcactgtca gaatcccggt gtctcgccca 660

atcctcatgc tcagggctcc cagggcccag gctgcagtgg aggatgtgct ggagcttcac 720

tgtgaggccc tgagaggctc tcctccaatc ctgtactggt tttatcacga ggatatcacc 780

ctggggagca ggtcggcccc ctctggagga ggagcctcct tcaacctttc cctgactgaa 840

gaacattctg gaaactactc ctgtgaggcc aacaatggcc tgggggccca gcgcagtgag 900

gcggtgacac tcaacttcac agtgcctact ggggccagaa gcaatcatct tacctcagga 960

gtcattgagg ggctgctcag cacccttggt ccagccaccg tggccttatt attttgctac 1020

ggcctcaaaa gaaaaatagg aagacgttca gccagggatc cactcaggag ccttcccagc 1080

cctctacccc aagagttcac ctacctcaac tcacctaccc cagggcagct acagcctata 1140

tatgaaaatg tgaatgttgt aagtggggat gaggtttatt cactggcgta ctataaccag 1200

ccggagcagg aatcagtagc agcagaaacc ctggggacac atatggagga caaggtttcc 1260

ttagacatct attccaggct gaggaaagca aacattacag atgtggacta tgaagatgct 1320

atgtaaggtt atggaagatt ctgctctttg aaaaccatcc atgaccccaa gcctcaggcc 1380

tgatatgttc ttcagagatc ctggggcatt agctttccag tatacctctt ctggatgcca 1440

ttctccatgg cactattcct tcatctactg tgaagtgaag ttggcgcagc cctgaagaaa 1500

ctacctagga gaactaatag acacaggagt gacagggact ttgttatcag aaccagattc 1560

ctgccggctc ctttgaaaac aggtcatatt gtgctcttct gtttacaaga ggaaacaaga 1620

tggaataaaa gaaattggga tcttgggttg gagggacagt gaagcttaga gcacatgaac 1680

tcaaggttag tgactctgca ggacttcaca gagagagctg tgcccatcat tcagtccaag 1740

tgctttctct gcccagacag cacagaactc cagccccgct acttacatgg atcatcgagt 1800

ttccacctaa aatatgattc tatttatttt gagtcactgt taccaaatta gaactaaaac 1860

aaagttacat aaaaagttat tgtgactcca cttaatttta gtgacgtatt tttgtatata 1920

taggccaacc tataccacat ccaaaattat gtatctatta cagcccctag aagctttata 1980

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aatacagtgt gtcttctttt attcacaaaa tttttgaaat cgtggtaata tggtttgaaa 2040

cctgtatctt aattatttttt ttttttaaatt gagacagggt ctcactctgt cactcaatct 2100

ggaatgcagt ggcacaatct tgcctcactg caacgcctgc ctctcaggct caagcaaacc 2160

tctcacctca gcctgctgag tagctgggac tacaggcaca tgccaccaaa cttggccatt 2220

ttttgtctta cgtagagaca agatttcacc gttttgccca ggctggtctc aaactcctgg 2280

gctcaagcaa tgtattgaat ttt 2303

<210> SEQ ID NO 11
<211> LENGTH: 90
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

gggcctgaca gcaacttttc ttctactagt tcatcttaac tttatcctgg taactggcga 60

gacaacctgt cttaagtaac tgaagggaaa 90

<210> SEQ ID NO 12
<211> LENGTH: 90
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

gggcctgaca gcaacttttc ttctactagt tcatcttaac acactgctct gtacggggca 60

cgtgggcaca ggtgcacact cacactcaca 90

<210> SEQ ID NO 13
<211> LENGTH: 90
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

tcccactgac gcatgcagga aggggcacct ccccttaacc acactgctct gtacggggca 60

cgtgggcaca ggtgcacact cacactcaca 90

<210> SEQ ID NO 14
<211> LENGTH: 2499
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

ctcaatcagc tttatgcaga gaagaagctt actgagctca ctgctggtgc tggtgtaggc 60

aagtgctgct ttggcaatct gggctgacct ggcttgtctc ctcagaactc cttctccaac 120

cctggagcag gcttccatgc tgctgtgggc gtccttgctg gcctttgctc cagtctgtgg 180

acaatctgca gctgcacaca aacctgtgat ttccgtccat cctccatgga ccacattctt 240

caaaggagag agagtgactc tgacttgcaa tggatttcag ttctatgcaa cagagaaaac 300

aacatggtat catcggcact actggggaga aaagttgacc ctgaccccag gaaacaccct 360

cgaggttcgg gaatctggac tgtacagatg ccaggcccgg ggctccccac gaagtaaccc 420

tgtgcgcttg ctcttttctt cagactcctt aatcctgcag gcaccatatt ctgtgtttga 480

aggtgacaca ttggttctga gatgccacag aagaaggaaa gagaaattga ctgctgtgaa 540

atatacttgg aatggaaaca ttctttccat ttctaataaa agctgggatc ttcttatccc 600

acaagcaagt tcaaataaca atggcaatta tcgatgcatt ggatatggag atgagaatga 660

tgtatttaga tcaaatttca aaataattaa aattcaagaa ctatttccac atccagagct 720

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gaaagctaca gactctcagc ctacagaggg gaattctgta aacctgagct gtgaaacaca 780

gcttcctcca gagcggtcag acaccccact tcacttcaac ttcttcagag atggcgaggt 840

catcctgtca gactggagca cgtacccgga actccagctc ccaaccgtct ggagagaaaa 900

ctcaggatcc tattggtgtg gtgctgaaac agtgaggggt aacatccaca agcacagtcc 960

ctcgctacag atccatgtgc agcggatccc tgtgtctggg gtgctcctgg agacccagcc 1020

ctcaggggggc caggctgttg aaggggagat gctggtcctt gtctgctccg tggctgaagg 1080

cacaggggat accacattct cctggcaccg agaggacatg caggagagtc tggggaggaa 1140

aactcagcgt tccctgagag cagagctgga gctccctgcc atcagacaga gccatgcagg 1200

gggatactac tgtacagcag acaacagcta cggccctgtc cagagcatgg tgctgaatgt 1260

cactgtgaga gagaccccag gcaacagaga tggccttgtc gccgcgggag ccactggagg 1320

gctgctcagt gctcttctcc tggctgtggc cctgctgttt cactgctggc gtcggaggaa 1380

gtcaggagtt ggtttcttgg gagacgaaac caggctccct cccgctccag gcccaggaga 1440

gtcctcccat tccatctgcc ctgcccaggt ggagcttcag tcgttgtatg ttgatgtaca 1500

ccccaaaaag ggagatttgg tatactctga gatccagact actcagctgg gagaagaaga 1560

ggaagctaat acctccagga cacttctaga ggataaggat gtctcagttg tctactctga 1620

ggtaaagaca caacacccag ataactcagc tggaaagatc agctctaagg atgaagaaag 1680

ttaagagaat gaaaagttac gggaacgtcc tactcatgtg atttctccct tgtccaaagt 1740

cccaggccca gtgcagtcct tgcggcacct ggaatgatca actcattcca gctttctaat 1800

tcttctcatg catatgcatt cactcccagg aatactcatt cgtctactct gatgttggga 1860

tggaatggcc tctgaaagac ttcactaaaa tgaccaggat ccacagttaa gagaagaccc 1920

tgtagtattt gctgtgggcc tgacctaatg cattccctag ggtctgcttt agagaagggg 1980

gataaagaga gagaaggact gttatgaaaa acagaagcac aaattttggt gaattgggat 2040

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tctcactgga gactcacttg catcagtttg tttaactgtg agtggctgca caggcactgt 2160

gcaaacaatg aaaagcccct tcacttctgc ctgcacagct tacactgtca ggattcagtt 2220

gcagattaaa gaacccatct ggaatggttt acagagagag gaatttaaaa gaggacatca 2280

gaagagctgg agatgcaagc tctaggctgc gcttccaaaa gcaaatgata attatgttaa 2340

tgtcattagt gacaaagatt tgcaacatta gagaaaagag acacaaatat aaaattaaaa 2400

acttaagtac caactctcca aaactaaatt tgaacttaaa atattagtat aaactcataa 2460

taaactctgc ctttaaataa aaaaaaaaaa aaaaaaaaa 2499

<210> SEQ ID NO 15
<211> LENGTH: 515
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Met Leu Leu Trp Ala Ser Leu Leu Ala Phe Ala Pro Val Cys Gly Gln
1 5 10 15

Ser Ala Ala Ala His Lys Pro Val Ile Ser Val His Pro Pro Trp Thr
20 25 30

Thr Phe Phe Lys Gly Glu Arg Val Thr Leu Thr Cys Asn Gly Phe Gln
35 40 45

Phe Tyr Ala Thr Glu Lys Thr Thr Trp Tyr His Arg His Tyr Trp Gly

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    50                  55                  60

Glu Lys Leu Thr Leu Thr Pro Gly Asn Thr Leu Glu Val Arg Glu Ser
65                  70                  75                  80

Gly Leu Tyr Arg Cys Gln Ala Arg Gly Ser Pro Arg Ser Asn Pro Val
                85                  90                  95

Arg Leu Leu Phe Ser Ser Asp Ser Leu Ile Leu Gln Ala Pro Tyr Ser
            100                 105                 110

Val Phe Glu Gly Asp Thr Leu Val Leu Arg Cys His Arg Arg Arg Lys
        115                 120                 125

Glu Lys Leu Thr Ala Val Lys Tyr Thr Trp Asn Gly Asn Ile Leu Ser
    130                 135                 140

Ile Ser Asn Lys Ser Trp Asp Leu Leu Ile Pro Gln Ala Ser Ser Asn
145                 150                 155                 160

Asn Asn Gly Asn Tyr Arg Cys Ile Gly Tyr Gly Asp Glu Asn Asp Val
                165                 170                 175

Phe Arg Ser Asn Phe Lys Ile Ile Lys Ile Gln Glu Leu Phe Pro His
            180                 185                 190

Pro Glu Leu Lys Ala Thr Asp Ser Gln Pro Thr Glu Gly Asn Ser Val
        195                 200                 205

Asn Leu Ser Cys Glu Thr Gln Leu Pro Pro Glu Arg Ser Asp Thr Pro
    210                 215                 220

Leu His Phe Asn Phe Phe Arg Asp Gly Glu Val Ile Leu Ser Asp Trp
225                 230                 235                 240

Ser Thr Tyr Pro Glu Leu Gln Leu Pro Thr Val Trp Arg Glu Asn Ser
                245                 250                 255

Gly Ser Tyr Trp Cys Gly Ala Glu Thr Val Arg Gly Asn Ile His Lys
            260                 265                 270

His Ser Pro Ser Leu Gln Ile His Val Gln Arg Ile Pro Val Ser Gly
        275                 280                 285

Val Leu Leu Glu Thr Gln Pro Ser Gly Gly Gln Ala Val Glu Gly Glu
    290                 295                 300

Met Leu Val Leu Val Cys Ser Val Ala Glu Gly Thr Gly Asp Thr Thr
305                 310                 315                 320

Phe Ser Trp His Arg Glu Asp Met Gln Glu Ser Leu Gly Arg Lys Thr
                325                 330                 335

Gln Arg Ser Leu Arg Ala Glu Leu Glu Leu Pro Ala Ile Arg Gln Ser
            340                 345                 350

His Ala Gly Gly Tyr Tyr Cys Thr Ala Asp Asn Ser Tyr Gly Pro Val
        355                 360                 365

Gln Ser Met Val Leu Asn Val Thr Val Arg Glu Thr Pro Gly Asn Arg
    370                 375                 380

Asp Gly Leu Val Ala Ala Gly Ala Thr Gly Gly Leu Leu Ser Ala Leu
385                 390                 395                 400

Ile Leu Ala Val Ala Leu Leu Phe His Cys Trp Arg Arg Arg Lys Ser
                405                 410                 415

Gly Val Gly Phe Leu Gly Asp Glu Thr Arg Leu Pro Pro Ala Pro Gly
            420                 425                 430

Pro Gly Glu Ser Ser His Ser Ile Cys Pro Ala Gln Val Glu Leu Gln
        435                 440                 445

Ser Leu Tyr Val Asp Val His Pro Lys Lys Gly Asp Leu Val Tyr Ser
    450                 455                 460

Glu Ile Gln Thr Thr Gln Leu Gly Glu Glu Glu Glu Ala Asn Thr Ser
465                 470                 475                 480
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Arg Thr Leu Leu Glu Asp Lys Asp Val Ser Val Val Tyr Ser Glu Val
485 490 495

Lys Thr Gln His Pro Asp Asn Ser Ala Gly Lys Ile Ser Ser Lys Asp
500 505 510

Glu Glu Ser
515

<210> SEQ ID NO 16
<211> LENGTH: 2805
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

cggtgcagtg tcctgactgt aagatcaagt ccaaacctgt tttggaattg aggaaacttc 60

tcttttgatc tcagcccttg gtggtccagg tcttcatgct gctgtgggtg atattactgg 120

tcctggctcc tgtcagtgga cagtttgcaa ggacacccag gcccattatt ttcctccagc 180

ctccatggac cacagtcttc caaggagaga gagtgaccct cacttgcaag ggatttcgct 240

tctactcacc acagaaaaca aaatggtacc atcggtacct tgggaaagaa atactaagag 300

aaaccccaga caatatcctt gaggttcagg aatctggaga gtacagatgc caggcccagg 360

gctcccctct cagtagccct gtgcacttgg atttttcttc agcttcgctg atcctgcaag 420

ctccactttc tgtgtttgaa ggagactctg tggttctgag gtgccgggca aaggcggaag 480

taacactgaa taatactatt tacaagaatg ataatgtcct ggcattcctt aataaaagaa 540

ctgacttcca tattcctcat gcatgtctca aggacaatgg tgcatatcgc tgtactggat 600

ataaggaaag ttgttgccct gtttcttcca atacagtcaa aatccaagtc caagagccat 660

ttacacgtcc agtgctgaga gccagctcct tccagcccat cagcgggaac ccagtgaccc 720

tgacctgtga gacccagctc tctctagaga ggtcagatgt cccgctccgg ttccgcttct 780

tcagagatga ccagaccctg ggattaggct ggagtctctc cccgaatttc cagattactg 840

ccatgtggag taaagattca gggttctact ggtgtaaggc agcaacaatg cctcacagcg 900

tcatatctga cagcccgaga tcctggatac aggtgcagat ccctgcatct catcctgtcc 960

tcactctcag ccctgaaaag gctctgaatt ttgagggaac caaggtgaca cttcactgtg 1020

aaacccagga agattctctg cgcactttgt acaggtttta tcatgagggt gtcccctga 1080

ggcacaagtc agtccgctgt gaaaggggag catccatcag cttctcactg actacagaga 1140

attcagggaa ctactactgc acagctgaca atggccttgg cgccaagccc agtaaggctg 1200

tgagcctctc agtcactgtt cccgtgtctc atcctgtcct caacctcagc tctcctgagg 1260

acctgatttt tgagggagcc aaggtgacac ttcactgtga agcccagaga ggttcactcc 1320

ccatcctgta ccagtttcat catgaggatg ctgccctgga gcgtaggtcg gccaactctg 1380

caggaggagt ggccatcagc ttctctctga ctgcagagca ttcagggaac tactactgca 1440

cagctgacaa tggctttggc ccccagcgca gtaaggcggt gagcctctcc atcactgtcc 1500

ctgtgtctca tcctgtcctc accctcagct ctgctgaggc cctgactttt gaaggagcca 1560

ctgtgacact tcactgtgaa gtccagagag gttccccaca aatcctatac cagttttatc 1620

atgaggacat gcccctgtgg agcagctcaa caccctctgt gggaagagtg tccttcagct 1680

tctctctgac tgaaggacat tcagggaatt actactgcac agctgacaat ggctttggtc 1740

cccagcgcag tgaagtggtg agccttttttg tcactgttcc agtgtctcgc cccatcctca 1800

ccctcagggt tcccagggcc caggctgtgg tgggggacct gctggagctt cactgtgagg 1860

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gcagctcagc cccctctgga ggagaagctt ctttcaacct ctctctgact gcagaacatt 1980

ctggaaacta ctcatgtgag gccaacaatg gcctagtggc ccagcacagt gacacaatat 2040

cactcagtgt tatagttcca gtatctcgtc ccatcctcac cttcagggct cccagggccc 2100

aggctgtggt gggggacctg ctggagcttc actgtgaggc cctgagaggc tcctccccaa 2160

tcctgtactg gttttatcat gaagatgtca ccctgggtaa gatctcagcc ccctctggag 2220

gaggggcctc cttcaacctc tctctgacta cagaacattc tggaatctac tcctgtgagg 2280

cagacaatgg tctggaggcc cagcgcagtg agatggtgac actgaaagtt gcaggtgagt 2340

gggccctgcc caccagcagc acatctgaga actgactgtg cctgttctcc ctgcagctga 2400

aaatggagcc acagagctcc tcagggctgt ttgcttgtgt ggcatcccag cacacttcct 2460

gcctgcagaa cctccctgtg aaagtctcgg atcctttgtg gtatggttcc aggaatctga 2520

tgtttcccag cagtcttctt gaagatgatc aaagcacctc actaaaaatg caaataagac 2580

ttttttagaa cataaactat attctgaact gaaattatta catgaaaatg aaaccaaaga 2640

attctgagca tatgtttctc tgccgtagaa aggattaagc tgtttcttgt ccggattctt 2700

ctctcattga cttctaagaa gcctctactc ttgagtctct ttcattactg gggatgtaaa 2760

tgttccttac atttccacat taaaaatcct atgttaacga aaaaa 2805

<210> SEQ ID NO 17
<211> LENGTH: 759
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Met Leu Leu Trp Val Ile Leu Leu Val Leu Ala Pro Val Ser Gly Gln
1 5 10 15

Phe Ala Arg Thr Pro Arg Pro Ile Ile Phe Leu Gln Pro Pro Trp Thr
20 25 30

Thr Val Phe Gln Gly Glu Arg Val Thr Leu Thr Cys Lys Gly Phe Arg
35 40 45

Phe Tyr Ser Pro Gln Lys Thr Lys Trp Tyr His Arg Tyr Leu Gly Lys
50 55 60

Glu Ile Leu Arg Glu Thr Pro Asp Asn Ile Leu Glu Val Gln Glu Ser
65 70 75 80

Gly Glu Tyr Arg Cys Gln Ala Gln Gly Ser Pro Leu Ser Ser Pro Val
85 90 95

His Leu Asp Phe Ser Ser Ala Ser Leu Ile Leu Gln Ala Pro Leu Ser
100 105 110

Val Phe Glu Gly Asp Ser Val Val Leu Arg Cys Arg Ala Lys Ala Glu
115 120 125

Val Thr Leu Asn Asn Thr Ile Tyr Lys Asn Asp Asn Val Leu Ala Phe
130 135 140

Leu Asn Lys Arg Thr Asp Phe His Ile Pro His Ala Cys Leu Lys Asp
145 150 155 160

Asn Gly Ala Tyr Arg Cys Thr Gly Tyr Lys Glu Ser Cys Cys Pro Val
165 170 175

Ser Ser Asn Thr Val Lys Ile Gln Val Gln Glu Pro Phe Thr Arg Pro
180 185 190

Val Leu Arg Ala Ser Ser Phe Gln Pro Ile Ser Gly Asn Pro Val Thr
195 200 205

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Leu Thr Cys Glu Thr Gln Leu Ser Leu Glu Arg Ser Asp Val Pro Leu
    210                 215                 220

Arg Phe Arg Phe Phe Arg Asp Asp Gln Thr Leu Gly Leu Gly Trp Ser
225                 230                 235                 240

Leu Ser Pro Asn Phe Gln Ile Thr Ala Met Trp Ser Lys Asp Ser Gly
                245                 250                 255

Phe Tyr Trp Cys Lys Ala Ala Thr Met Pro His Ser Val Ile Ser Asp
            260                 265                 270

Ser Pro Arg Ser Trp Ile Gln Val Gln Ile Pro Ala Ser His Pro Val
        275                 280                 285

Leu Thr Leu Ser Pro Glu Lys Ala Leu Asn Phe Glu Gly Thr Lys Val
    290                 295                 300

Thr Leu His Cys Glu Thr Gln Glu Asp Ser Leu Arg Thr Leu Tyr Arg
305                 310                 315                 320

Phe Tyr His Glu Gly Val Pro Leu Arg His Lys Ser Val Arg Cys Glu
                325                 330                 335

Arg Gly Ala Ser Ile Ser Phe Ser Leu Thr Thr Glu Asn Ser Gly Asn
            340                 345                 350

Tyr Tyr Cys Thr Ala Asp Asn Gly Leu Gly Ala Lys Pro Ser Lys Ala
        355                 360                 365

Val Ser Leu Ser Val Thr Val Pro Val Ser His Pro Val Leu Asn Leu
    370                 375                 380

Ser Ser Pro Glu Asp Leu Ile Phe Glu Gly Ala Lys Val Thr Leu His
385                 390                 395                 400

Cys Glu Ala Gln Arg Gly Ser Leu Pro Ile Leu Tyr Gln Phe His His
                405                 410                 415

Glu Asp Ala Ala Leu Glu Arg Arg Ser Ala Asn Ser Ala Gly Gly Val
            420                 425                 430

Ala Ile Ser Phe Ser Leu Thr Ala Glu His Ser Gly Asn Tyr Tyr Cys
        435                 440                 445

Ala Thr Asp Asn Gly Phe Gly Pro Gln Arg Ser Lys Ala Val Ser Leu
    450                 455                 460

Ser Ile Thr Val Pro Val Ser His Pro Val Leu Thr Leu Ser Ser Ala
465                 470                 475                 480

Glu Ala Leu Thr Phe Glu Gly Ala Thr Val Thr Leu His Cys Glu Val
                485                 490                 495

Gln Arg Gly Ser Pro Gln Ile Leu Tyr Gln Phe Tyr His Glu Asp Met
            500                 505                 510

Pro Leu Trp Ser Ser Ser Thr Pro Ser Val Gly Arg Val Ser Phe Ser
        515                 520                 525

Phe Ser Leu Thr Glu Gly His Ser Gly Asn Tyr Tyr Cys Thr Ala Asp
    530                 535                 540

Asn Gly Phe Gly Pro Gln Arg Ser Glu Val Val Ser Leu Phe Val Thr
545                 550                 555                 560

Val Pro Val Ser Arg Pro Ile Leu Thr Leu Arg Val Pro Arg Ala Gln
                565                 570                 575

Ala Val Val Gly Asp Leu Leu Glu Leu His Cys Glu Ala Pro Arg Gly
            580                 585                 590

Ser Pro Pro Ile Leu Tyr Trp Phe Tyr His Glu Asp Val Thr Leu Gly
        595                 600                 605

Ser Ser Ser Ala Pro Ser Gly Gly Glu Ala Ser Phe Asn Leu Ser Leu
    610                 615                 620
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Thr Ala Glu His Ser Gly Asn Tyr Ser Cys Glu Ala Asn Asn Gly Leu
625                 630                 635                 640

Val Ala Gln His Ser Asp Thr Ile Ser Leu Ser Val Ile Val Pro Val
                645                 650                 655

Ser Arg Pro Ile Leu Thr Phe Arg Ala Pro Arg Ala Gln Ala Val Val
            660                 665                 670

Gly Asp Leu Leu Glu Leu His Cys Glu Ala Leu Arg Gly Ser Ser Pro
        675                 680                 685

Ile Leu Tyr Trp Phe Tyr His Glu Asp Val Thr Leu Gly Lys Ile Ser
    690                 695                 700

Ala Pro Ser Gly Gly Gly Ala Ser Phe Asn Leu Ser Leu Thr Thr Glu
705                 710                 715                 720

His Ser Gly Ile Tyr Ser Cys Glu Ala Asp Asn Gly Leu Glu Ala Gln
                725                 730                 735

Arg Ser Glu Met Val Thr Leu Lys Val Ala Gly Glu Trp Ala Leu Pro
            740                 745                 750

Thr Ser Ser Thr Ser Glu Asn
        755
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<210> SEQ ID NO 18
<211> LENGTH: 4448
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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tcttttgatc tcagcccttg gtggtccagg tcttcatgct gctgtgggtg atattactgg    120

tcctggctcc tgtcagtgga cagtttgcaa ggacacccag gcccattatt ttcctccagc    180

ctccatggac cacagtcttc caaggagaga gagtgaccct cacttgcaag ggatttcgct    240

tctactcacc acagaaaaca aaatggtacc atcggtacct tgggaaagaa atactaagag    300

aaaccccaga caatatcctt gaggttcagg aatctggaga gtacagatgc caggcccagg    360

gctcccctct cagtagccct gtgcacttgg atttttcttc agcttcgctg atcctgcaag    420

ctccactttc tgtgtttgaa ggagactctg tggttctgag gtgccgggca aaggcggaag    480

taacactgaa taatactatt tacaagaatg ataatgtcct ggcattcctt aataaaagaa    540

ctgacttcca tattcctcat gcatgtctca aggacaatgg tgcatatcgc tgtactggat    600

ataaggaaag ttgttgccct gtttcttcca atacagtcaa aatccaagtc caagagccat    660

ttacacgtcc agtgctgaga gccagctcct tccagcccat cagcgggaac ccagtgaccc    720

tgacctgtga gacccagctc tctctagaga ggtcagatgt cccgctccgg ttccgcttct    780

tcagagatga ccagaccctg ggattaggct ggagtctctc cccgaatttc cagattactg    840

ccatgtggag taaagattca gggttctact ggtgtaaggc agcaacaatg cctcacagcg    900

tcatatctga cagcccgaga tcctggatac aggtgcagat ccctgcatct catcctgtcc    960

tcactctcag ccctgaaaag gctctgaatt ttgagggaac caaggtgaca cttcactgtg   1020

aaacccagga agattctctg cgcactttgt acaggtttta tcatgagggt gtccccctga   1080

ggcacaagtc agtccgctgt gaaaggggag catccatcag cttctcactg actacagaga   1140

attcagggaa ctactactgc acagctgaca atggccttgg cgccaagccc agtaaggctg   1200

tgagcctctc agtcactgtt cccgtgtctc atcctgtcct caacctcagc tctcctgagg   1260

acctgatttt tgagggagcc aaggtgacac ttcactgtga agcccagaga ggttcactcc   1320
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ccatcctgta ccagtttcat catgaggatg ctgccctgga gcgtaggtcg gccaactctg 1380

caggaggagt ggccatcagc ttctctctga ctgcagagca ttcagggaac tactactgca 1440

cagctgacaa tggctttggc ccccagcgca gtaaggcggt gagcctctcc atcactgtcc 1500

ctgtgtctca tcctgtcctc accctcagct ctgctgaggc cctgactttt gaaggagcca 1560

ctgtgacact tcactgtgaa gtccagagag gttccccaca aatcctatac cagttttatc 1620

atgaggacat gcccctgtgg agcagctcaa caccctctgt gggaagagtg tccttcagct 1680

tctctctgac tgaaggacat tcagggaatt actactgcac agctgacaat ggctttggtc 1740

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acccacccct ggctgagttc tctctcaccc attcctttaa aaatctgttt gcactgtcca 1860

gtttcctccc ctaatcaact taatcccctt cttggcttcc tcctcaacta actagctggg 1920

gttttccgta ctcataagtc ctggctcagc cagaccccta aaacagctca gtagattccc 1980

cagcttttac caaatgaatt tatttattgt attttctcct cattccttgt atgttccaac 2040

agtacgccaa ttttttcttga tgcacggagc gtgtcctact tctctactga catttacata 2100

ttaacttagc tacaagcaca gtcttataga taaatattgg tcaagacctt aaattctcca 2160

aaggatttcc aatcttatgg tagatttgga gaaagctgct ggtgaacaaa gggggaaatg 2220

gctccctagg aaccaactcc tcaaacttct ggagttttta tgatcccttg ttttctaacc 2280

tgctaaaatc agtatcattt tattgtatta ttttaaaaaa actattgttg aagtatgaca 2340

tacattcaag aaacgtgtgc aaattgtatg tgtacgattt ggtgtctttt taggagctaa 2400

gttgcttctg ttttttacttg aatctttgtt tatagaaact gggggaaagt ttactttctt 2460

ttcagagaag ccaaatggta tgatagaaaa atcttgagcc tgatgtgtca gacatgcccc 2520

tagcataact tgttgagtaa agaggttatt tttaaaatgt gaatgttctg agactactcc 2580

aaagtcagag ccaaatctac taggaagctt ctagacttca ctcattctgc atcccattac 2640

tatcttttta tccatgtttt actttcttct catattcagc agcatcttaa gcctctttat 2700

tttctgtttc ttgactgtca cccttaatgc cagtagaatg taagcttcat gagaacagaa 2760

ctgcatccat cttggtcttc acaacatccc tgtgcctact cagtgtttgg cacacagtag 2820

gtcctcagtc aacatttgta atttagtgga cagatgatat gacaagatga taagagggga 2880

tttaaaaaaa tcatctagca aagcccaaga ggaaaaaaaa caaagctatt ttagaaatga 2940

aataccaatt tgaagcagta agaatagatt ggatatcttt gaaaaccatt aattgaatga 3000

agaaccaatt tgagaaaaca atacagaatg caaagtagaa agatacagaa ataaaggcaa 3060

aagttataat atggaaatca gacaatggat ttgtctgtat ccagttatgt ggataattaa 3120

aatggagacc ctcagaaaat tgaaccgaag agtaaaatga aactcaaaaa tgtagtagaa 3180

attgttggga agtaaagaaa acttgaatat gtagatcaga acatatatgt tgatgacgtt 3240

attgactttg aggttaaaaa tatatatatg tgcctatgat tatggggaaa aaagcagtcg 3300

tctcagaaag aaaaacatca agttagtctt agactttgca gtgcactcag taccaaagag 3360

agaggaggcc agacttggac ctgcgaggga agaataataa ccgaaaattt tatatcaatt 3420

caaaaagaca ttgtcaaaaa tacagggatt caggaaactg agaatgcact aagccttctg 3480

gaaaaaacac ctaatgacaa aatctagccc aacaagatgt aaatgaatat aaaggactca 3540

taatgaggaa accgcattat gactggctct caaccctggc cgcatattag actcgtcaaa 3600

gacctttgta aaaggtcaca cattgactcg tcaaagcccc tctccagact aattcaattc 3660

agaatctcac agatggggcc acagaatcag tatttttga cacaacctca agtgagaata 3720

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ttgtgtagac aagattggaa accactgatt tagatataga aacaaaggct aatcaactgt   3780

gagaattatg gtcacagaat agaaagtaac tattatgaac actgaaaatg taaaaaaaat   3840

gtaacaaaga aaaatagtta gaggaaggag aggaagtaaa ggaacaatca ttttctcatg   3900

attattatta tttcagagta aattgtgagt tatttcacaa ttcaaaaaga atggactgtt   3960

ttaaaaaatt agtaatagat ttcaaaatgt ccattttgta aatcgtttct gaatactttg   4020

tcaacagtta ctcatcatta atggcttata cttcactaaa attccatgga aaaccaacta   4080

gtagcctgta gagtcacata ggagagaaca agtgaattct ttgggtggcg caagcataga   4140

tgttaggact gacaaaaaaa aataataaaa ataaacctgt gcattgatat gatcacaaat   4200

gatcagggaa agaggaaaca gaaactctca tacgccatta ttacaagtgt aaattggttc   4260

aacctttttcg tcttaattga cacattgtaa ttgtatatat ttatggaagc acagtttgat   4320

attttgatat acatacatgg tatataacga tcaaattagg atatttaatg tacccatcat   4380

ctcatgcatt tatcatttct ttggaataaa aacattcaaa agccaaaaaa aaaaaaaaaa   4440

aaaaaaaa                                                           4448
```

<210> SEQ ID NO 19
<211> LENGTH: 592
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

```
Met Leu Leu Trp Val Ile Leu Leu Val Leu Ala Pro Val Ser Gly Gln
1               5                   10                  15

Phe Ala Arg Thr Pro Arg Pro Ile Ile Phe Leu Gln Pro Pro Trp Thr
            20                  25                  30

Thr Val Phe Gln Gly Glu Arg Val Thr Leu Thr Cys Lys Gly Phe Arg
        35                  40                  45

Phe Tyr Ser Pro Gln Lys Thr Lys Trp Tyr His Arg Tyr Leu Gly Lys
    50                  55                  60

Glu Ile Leu Arg Glu Thr Pro Asp Asn Ile Leu Glu Val Gln Glu Ser
65                  70                  75                  80

Gly Glu Tyr Arg Cys Gln Ala Gln Gly Ser Pro Leu Ser Ser Pro Val
                85                  90                  95

His Leu Asp Phe Ser Ser Ala Ser Leu Ile Leu Gln Ala Pro Leu Ser
            100                 105                 110

Val Phe Glu Gly Asp Ser Val Val Leu Arg Cys Arg Ala Lys Ala Glu
        115                 120                 125

Val Thr Leu Asn Asn Thr Ile Tyr Lys Asn Asp Asn Val Leu Ala Phe
    130                 135                 140

Leu Asn Lys Arg Thr Asp Phe His Ile Pro His Ala Cys Leu Lys Asp
145                 150                 155                 160

Asn Gly Ala Tyr Arg Cys Thr Gly Tyr Lys Glu Ser Cys Cys Pro Val
                165                 170                 175

Ser Ser Asn Thr Val Lys Ile Gln Val Gln Glu Pro Phe Thr Arg Pro
            180                 185                 190

Val Leu Arg Ala Ser Ser Phe Gln Pro Ile Ser Gly Asn Pro Val Thr
        195                 200                 205

Leu Thr Cys Glu Thr Gln Leu Ser Leu Glu Arg Ser Asp Val Pro Leu
    210                 215                 220

Arg Phe Arg Phe Phe Arg Asp Asp Gln Thr Leu Gly Leu Gly Trp Ser
225                 230                 235                 240
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Leu Ser Pro Asn Phe Gln Ile Thr Ala Met Trp Ser Lys Asp Ser Gly
                245                 250                 255

Phe Tyr Trp Cys Lys Ala Ala Thr Met Pro His Ser Val Ile Ser Asp
            260                 265                 270

Ser Pro Arg Ser Trp Ile Gln Val Gln Ile Pro Ala Ser His Pro Val
        275                 280                 285

Leu Thr Leu Ser Pro Glu Lys Ala Leu Asn Phe Glu Gly Thr Lys Val
    290                 295                 300

Thr Leu His Cys Glu Thr Gln Glu Asp Ser Leu Arg Thr Leu Tyr Arg
305                 310                 315                 320

Phe Tyr His Glu Gly Val Pro Leu Arg His Lys Ser Val Arg Cys Glu
                325                 330                 335

Arg Gly Ala Ser Ile Ser Phe Ser Leu Thr Thr Glu Asn Ser Gly Asn
            340                 345                 350

Tyr Tyr Cys Thr Ala Asp Asn Gly Leu Gly Ala Lys Pro Ser Lys Ala
        355                 360                 365

Val Ser Leu Ser Val Thr Val Pro Val Ser His Pro Val Leu Asn Leu
    370                 375                 380

Ser Ser Pro Glu Asp Leu Ile Phe Glu Gly Ala Lys Val Thr Leu His
385                 390                 395                 400

Cys Glu Ala Gln Arg Gly Ser Leu Pro Ile Leu Tyr Gln Phe His His
                405                 410                 415

Glu Asp Ala Ala Leu Glu Arg Arg Ser Ala Asn Ser Ala Gly Gly Val
            420                 425                 430

Ala Ile Ser Phe Ser Leu Thr Ala Glu His Ser Gly Asn Tyr Tyr Cys
        435                 440                 445

Thr Ala Asp Asn Gly Phe Gly Pro Gln Arg Ser Lys Ala Val Ser Leu
    450                 455                 460

Ser Ile Thr Val Pro Val Ser His Pro Val Leu Thr Leu Ser Ser Ala
465                 470                 475                 480

Glu Ala Leu Thr Phe Glu Gly Ala Thr Val Thr Leu His Cys Glu Val
                485                 490                 495

Gln Arg Gly Ser Pro Gln Ile Leu Tyr Gln Phe Tyr His Glu Asp Met
            500                 505                 510

Pro Leu Val Ser Ser Ser Thr Pro Ser Val Gly Arg Val Ser Phe Ser
        515                 520                 525

Phe Ser Leu Thr Glu Gly His Ser Gly Asn Tyr Tyr Cys Thr Ala Asp
    530                 535                 540

Asn Gly Phe Gly Pro Gln Arg Ser Glu Val Val Ser Leu Phe Val Thr
545                 550                 555                 560

Gly Lys Cys Trp Val Leu Ala Ser Lys Pro Pro Leu Ala Glu Phe Ser
                565                 570                 575

Leu Thr His Ser Phe Lys Asn Leu Phe Ala Leu Ser Ser Phe Leu Pro
            580                 585                 590


<210> SEQ ID NO 20
<211> LENGTH: 5323
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

cggtgcagtg tcctgactgt aagatcaagt ccaaacctgt tttggaattg aggaaacttc     60

tcttttgatc tcagcccttg gtggtccagg tcttcatgct gctgtgggtg atattactgg    120
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tcctggctcc tgtcagtgga cagtttgcaa ggacacccag gcccattatt ttcctccagc 180

ctccatggac cacagtcttc caaggagaga gagtgaccct cacttgcaag ggatttcgct 240

tctactcacc acagaaaaca aaatggtacc atcggtacct tgggaaagaa atactaagag 300

aaaccccaga caatatcctt gaggttcagg aatctggaga gtacagatgc caggcccagg 360

gctcccctct cagtagccct gtgcacttgg atttttcttc agcttcgctg atcctgcaag 420

ctccactttc tgtgtttgaa ggagactctg tggttctgag gtgccgggca aaggcggaag 480

taacactgaa taatactatt tacaagaatg ataatgtcct ggcattcctt aataaaagaa 540

ctgacttcca tattcctcat gcatgtctca aggacaatgg tgcatatcgc tgtactggat 600

ataaggaaag ttgttgccct gtttcttcca atacagtcaa aatccaagtc caagagccat 660

ttacacgtcc agtgctgaga gccagctcct tccagcccat cagcgggaac ccagtgaccc 720

tgacctgtga gacccagctc tctctagaga ggtcagatgt cccgctccgg ttccgcttct 780

tcagagatga ccagaccctg ggattaggct ggagtctctc cccgaatttc cagattactg 840

ccatgtggag taaagattca gggttctact ggtgtaaggc agcaacaatg cctcacagcg 900

tcatatctga cagcccgaga tcctggatac aggtgcagat ccctgcatct catcctgtcc 960

tcactctcag ccctgaaaag gctctgaatt ttgagggaac caaggtgaca cttcactgtg 1020

aaacccagga agattctctg cgcactttgt acaggtttta tcatgagggt gtccccctga 1080

ggcacaagtc agtccgctgt gaaaggggag catccatcag cttctcactg actacagaga 1140

attcagggaa ctactactgc acagctgaca atggccttgg cgccaagccc agtaaggctg 1200

tgagcctctc agtcactgtt cccgtgtctc atcctgtcct caacctcagc tctcctgagg 1260

acctgatttt tgagggagcc aaggtgacac ttcactgtga agcccagaga ggttcactcc 1320

ccatcctgta ccagtttcat catgaggatg ctgccctgga gcgtaggtcg gccaactctg 1380

caggaggagt ggccatcagc ttctctctga ctgcagagca ttcagggaac tactactgca 1440

cagctgacaa tggctttggc ccccagcgca gtaaggcggt gagcctctcc atcactgtcc 1500

ctgtgtctca tcctgtcctc accctcagct ctgctgaggc cctgactttt gaaggagcca 1560

ctgtgacact tcactgtgaa gtccagagag gttccccaca aatcctatac cagttttatc 1620

atgaggacat gcccctgtgg agcagctcaa caccctctgt gggaagagtg tccttcagct 1680

tctctctgac tgaaggacat tcagggaatt actactgcac agctgacaat ggctttggtc 1740

cccagcgcag tgaagtggtg agccttttttg tcactgttcc agtgtctcgc cccatcctca 1800

ccctcagggt tcccagggcc caggctgtgg tgggggacct gctggagctt cactgtgagg 1860

ccccgagagg ctctccccca atcctgtact ggttttatca tgaggatgtc accctgggga 1920

gcagctcagc cccctctgga ggagaagctt ctttcaacct ctctctgact gcagaacatt 1980

ctggaaacta ctcatgtgag gccaacaatg gcctagtggc ccagcacagt gacacaatat 2040

cactcagtgt tatagttcca gtatctcgtc ccatcctcac cttcagggct cccagggccc 2100

aggctgtggt gggggacctg ctggagcttc actgtgaggc cctgagaggc tcctccccaa 2160

tcctgtactg gttttatcat gaagatgtca ccctgggtaa gatctcagcc ccctctggag 2220

gaggggcctc cttcaacctc tctctgacta cagaacattc tggaatctac tcctgtgagg 2280

cagacaatgg tctggaggcc cagcgcagtg agatggtgac actgaaagtt gcagttccgg 2340

tgtctcgccc ggtcctcacc ctcagggctc ccgggaccca tgctgcggtg ggggacctgc 2400

tggagcttca ctgtgaggcc ctgagaggct ctcccctgat cctgtaccgg ttttttcatg 2460

aggatgtcac cctaggaaat aggtcgtccc cctctggagg agcgtcctta aacctctctc 2520

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tgactgcaga gcactctgga aactactcct gtgaggccga caatggcctc ggggcccagc 2580

gcagtgagac agtgacactt tatatcacag ggctgaccgc gaacagaagt ggccctttg 2640

ccacaggagt cgccgggggc ctgctcagca tagcaggcct tgctgcgggg gcactgctgc 2700

tctactgctg gctctcgaga aaagcaggga gaaagcctgc ctctgacccc gccaggagcc 2760

cttcagactc ggactcccaa gagcccacct atcacaatgt accagcctgg gaagagctgc 2820

aaccagtgta cactaatgca aatcctagag gagaaaatgt ggtttactca gaagtacgga 2880

tcatccaaga gaaaaagaaa catgcagtgg cctctgaccc caggcatctc aggaacaagg 2940

gttcccctat catctactct gaagttaagg tggcgtcaac cccggtttcc ggatccctgt 3000

tcttggcttc ctcagctcct cacagatgag tccacacgtc tctccaactg ctgtttcagc 3060

ctctgcaccc caaagttccc cttgggggag aagcagcatt gaagtgggaa gatttaggct 3120

gccccagacc atatctactg gcctttgttt cacatgtcct cattctcagt ctgaccagaa 3180

tgcagggccc tgctggactg tcacctgttt cccagttaaa gccctgactg gcaggttttt 3240

taatccagtg gcaaggtgct cccactccag ggcccagcac atctcctgga ttccttagtg 3300

ggcttcagct gtggttgctg ttctgagtac tgctctcatc acacccccac agaggggtc 3360

ttaccacaca aagggagagt gggccttcag gagatgccgg gctggcctaa cagctcaggt 3420

gctcctaaac tccgacacag agttcctgct ttgggtggat gcatttctca attgtcatca 3480

gcctggtggg gctactgcag tgtgctgcca aatgggacag cacacagcct gtgcacatgg 3540

gacatgtgat gggtctcccc acgggggctg catttcacac tcctccacct gtctcaaact 3600

ctaaggtcgg cacttgacac caaggtaact tctctcctgc tcatgtgtca gtgtctacct 3660

gcccaagtaa gtggctttca tacaccaagt cccgaagttc ttcccatcct aacagaagta 3720

acccagcaag tcaaggccag gaggaccagg ggtgcagaca gaacacatac tggaacacag 3780

gaggtgctca attactattt gactgactga ctgaatgaat gaatgaatga ggaagaaaac 3840

tgtgggtaat caaactggca taaaatccag tgcactccct aggaaatccg ggaggtattc 3900

tggcttccta agaaacaacg gaagagaagg agcttggatg aagaaactgt tcagcaagaa 3960

gaagggcttc ttcacacttt tatgtgcttg tggatcacct gaggatctgt gaaaatacag 4020

atactgattc agtgggtctg tgtagagcct gagactgcca ttctaacatg ttcccagggg 4080

atgctgatgc tgctggccct gggactgcac tgcatgcatg tgaagcccta taggtctcag 4140

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cagggctgac tctgctgccc caacctttca aggaggaaac cagacacctg agacaggagc 4680

ctgtatgcag cccagtgcag ccttgcagag gacaaggctg gaggcatttg tcatcactac 4740

agatatgcaa ctaaaataga cgtggagcaa gagaaatgca ttcccaccga ggccgctttt 4800

ttaggcctag ttgaaagtca agaaggacag cagcaagcat aggctcagga ttaaagaaaa 4860

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```
aaatctgctc acagtctgtt ctggaggtca catcaccaac aaagctcacg ccctatgcag   4920

ttctgagaag gtggaggcac caggctcaaa agaggaaatt tagaatttct cattgggaga   4980

gtaaggtacc cccatcccag aatgataact gcacagtggc agaacaaact ccaccctaat   5040

gtgggtggac cccatccagt ctgttgaagg cctgaatgta acaaaagggc ttattcttcc   5100

tcaagtaagg gggaactcct gctttgggct gggacataag tttttctgct ttcagacgca   5160

aactgaaaaa tggctcttct tgggtcttga gcttgctggc atatggactg aaagaaacta   5220

tgctattgga tctcctggat ctccagcttg ctgactgcag atcttgagat atgtcagcct   5280

ctacagtcac aagagctaat tcattctaat aaaccaatct ttc                     5323
```

<210> SEQ ID NO 21
<211> LENGTH: 977
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

```
Met Leu Leu Trp Val Ile Leu Leu Val Leu Ala Pro Tyr Ser Gly Gln
1               5                   10                  15

Phe Ala Arg Thr Pro Arg Pro Ile Ile Phe Leu Gln Pro Pro Trp Thr
            20                  25                  30

Thr Val Phe Gln Gly Glu Arg Val Thr Leu Thr Cys Lys Gly Phe Arg
        35                  40                  45

Phe Tyr Ser Pro Gln Lys Thr Lys Trp Tyr His Arg Tyr Leu Gly Lys
    50                  55                  60

Glu Ile Leu Arg Glu Thr Pro Asp Asn Ile Leu Glu Val Gln Glu Ser
65                  70                  75                  80

Gly Ser Tyr Arg Cys Gln Ala Gln Gly Ser Pro Leu Ser Ser Pro Val
                85                  90                  95

His Leu Asp Phe Ser Ser Ala Ser Leu Ile Leu Gln Ala Pro Leu Ser
            100                 105                 110

Val Phe Glu Gly Asp Ser Val Val Leu Arg Cys Arg Ala Lys Ala Glu
        115                 120                 125

Val Thr Leu Asn Asn Thr Ile Tyr Lys Asn Asp Asn Val Leu Ala Phe
    130                 135                 140

Leu Asn Lys Arg Thr Asp Phe His Ile Pro His Ala Cys Leu Lys Asp
145                 150                 155                 160

Asn Gly Ala Tyr Arg Cys Thr Gly Tyr Lys Glu Ser Cys Cys Pro Val
                165                 170                 175

Ser Ser Asn Thr Val Lys Ile Gln Val Gln Glu Pro Phe Thr Arg Pro
            180                 185                 190

Val Leu Arg Ala Ser Ser Phe Gln Pro Ile Ser Gly Asn Pro Val Thr
        195                 200                 205

Leu Thr Cys Glu Thr Gln Leu Ser Leu Glu Arg Ser Asp Val Pro Leu
    210                 215                 220

Arg Phe Arg Phe Phe Arg Asp Asp Gln Thr Leu Gly Leu Gly Trp Ser
225                 230                 235                 240

Leu Ser Pro Asn Phe Gln Ile Thr Ala Met Trp Ser Lys Asp Ser Gly
                245                 250                 255

Phe Tyr Trp Cys Lys Ala Ala Thr Met Pro His Ser Val Ile Ser Asp
            260                 265                 270

Ser Pro Arg Ser Trp Ile Gln Val Gln Ile Pro Ala Ser His Pro Val
        275                 280                 285

Leu Thr Leu Ser Pro Glu Lys Ala Leu Asn Phe Glu Gly Thr Lys Val
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    290                 295                 300

Thr Leu His Cys Glu Thr Gln Glu Asp Ser Leu Arg Thr Leu Tyr Arg
305                 310                 315                 320

Phe Tyr His Glu Gly Val Pro Leu Arg His Lys Ser Val Arg Cys Glu
                325                 330                 335

Arg Gly Ala Ser Ile Ser Phe Ser Leu Thr Thr Glu Asn Ser Gly Asn
            340                 345                 350

Tyr Tyr Cys Thr Ala Asp Asn Gly Leu Gly Ala Lys Pro Ser Lys Ala
        355                 360                 365

Val Ser Leu Ser Val Thr Val Pro Val Ser His Pro Val Leu Asn Leu
    370                 375                 380

Ser Ser Pro Glu Asp Leu Ile Phe Glu Gly Ala Lys Val Thr Leu His
385                 390                 395                 400

Cys Glu Ala Gln Arg Gly Ser Leu Pro Ile Leu Tyr Gln Phe His His
                405                 410                 415

Glu Asp Ala Ala Leu Glu Arg Arg Ser Ala Asn Ser Ala Gly Gly Val
            420                 425                 430

Ala Ile Ser Phe Ser Leu Thr Ala Glu His Ser Gly Asn Tyr Tyr Cys
        435                 440                 445

Thr Ala Asp Asn Gly Phe Gly Pro Gln Arg Ser Lys Ala Val Ser Leu
    450                 455                 460

Ser Ile Thr Val Pro Val Ser His Pro Val Leu Thr Leu Ser Ser Ala
465                 470                 475                 480

Glu Ala Leu Thr Phe Glu Gly Ala Thr Val Thr Leu His Cys Glu Val
                485                 490                 495

Gln Arg Gly Ser Pro Gln Ile Leu Tyr Gln Phe Tyr His Glu Asp Met
            500                 505                 510

Pro Leu Trp Ser Ser Ser Thr Pro Ser Val Gly Arg Val Ser Phe Ser
        515                 520                 525

Phe Ser Leu Thr Glu Gly His Ser Gly Asn Tyr Tyr Cys Thr Ala Asp
    530                 535                 540

Asn Gly Phe Gly Pro Gln Arg Ser Glu Val Val Ser Leu Phe Val Thr
545                 550                 555                 560

Val Pro Val Ser Arg Pro Ile Leu Thr Leu Arg Val Pro Arg Ala Gln
                565                 570                 575

Ala Val Val Gly Asp Leu Leu Glu Leu His Cys Glu Ala Pro Arg Gly
            580                 585                 590

Ser Pro Pro Ile Leu Tyr Trp Phe Tyr His Glu Asp Val Thr Leu Gly
        595                 600                 605

Ser Ser Ser Ala Pro Ser Gly Gly Glu Ala Ser Phe Asn Leu Ser Leu
    610                 615                 620

Thr Ala Glu His Ser Gly Asn Tyr Ser Cys Glu Ala Asn Asn Gly Leu
625                 630                 635                 640

Val Ala Gln His Ser Asp Thr Ile Ser Leu Ser Val Ile Val Pro Val
                645                 650                 655

Ser Arg Pro Ile Leu Thr Phe Arg Ala Pro Arg Ala Gln Ala Val Val
            660                 665                 670

Gly Asp Leu Leu Glu Leu His Cys Glu Ala Leu Arg Gly Ser Ser Pro
        675                 680                 685

Ile Leu Tyr Trp Phe Tyr His Glu Asp Val Thr Leu Gly Lys Ile Ser
    690                 695                 700

Ala Pro Ser Gly Gly Gly Ala Ser Phe Asn Leu Ser Leu Thr Thr Glu
705                 710                 715                 720
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His Ser Gly Ile Tyr Ser Cys Glu Ala Asp Asn Gly Leu Glu Ala Gln
                725                 730                 735

Arg Ser Glu Met Val Thr Leu Lys Val Ala Val Pro Val Ser Arg Pro
            740                 745                 750

Val Leu Thr Leu Arg Ala Pro Gly Thr His Ala Ala Val Gly Asp Leu
        755                 760                 765

Leu Thr Glu Leu His Cys Glu Ala Leu Arg Gly Ser Pro Leu Ile Leu
    770                 775                 780

Tyr Arg Phe Phe His Glu Asp Val Thr Leu Gly Asn Glu Leu His Cys
785                 790                 795                 800

Glu Ala Leu Arg Gly Ser Pro Leu Ile Leu Tyr Arg Phe Phe His Glu
                805                 810                 815

Asp Val Thr Leu Gly Asn Asn Gly Leu Gly Ala Gln Arg Ser Glu Thr
            820                 825                 830

Val Thr Leu Tyr Ile Thr Gly Leu Thr Ala Asn Arg Ser Gly Pro Phe
        835                 840                 845

Ala Thr Gly Val Ala Gly Gly Leu Leu Ser Ile Ala Gly Leu Ala Ala
    850                 855                 860

Gly Ala Leu Leu Leu Tyr Cys Trp Leu Ser Arg Lys Ala Gly Arg Lys
865                 870                 875                 880

Pro Ala Ser Asp Pro Ala Arg Ser Pro Ser Asp Ser Asp Ser Gln Glu
                885                 890                 895

Pro Thr Tyr His Met Val Pro Ala Trp Glu Glu Leu Gln Pro Val Tyr
            900                 905                 910

Thr Asn Ala Asn Pro Arg Gly Glu Asn Val Val Tyr Ser Glu Val Arg
        915                 920                 925

Ile Ile Gln Glu Lys Lys Lys His Ala Val Ala Ser Asp Pro Arg His
    930                 935                 940

Leu Arg Asn Lys Gly Ser Pro Ile Ile Tyr Ser Glu Val Lys Val Ala
945                 950                 955                 960

Ser Thr Pro Val Ser Gly Ser Leu Phe Leu Ala Ser Ser Ala Pro His
                965                 970                 975

Arg
```

<210> SEQ ID NO 22
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

```
Met Leu Leu Trp Ala Ser Leu Leu Ala Phe Ala Pro Val Cys Gly Gln
1               5                   10                  15

Ser Gly Ser Cys Ser Val Ala Asp Trp Gln Met Pro Pro Pro Tyr Val
            20                  25                  30

Val Leu Asp Leu Pro Gln Glu Thr Leu Glu Glu Glu Thr Pro Gly Ala
        35                  40                  45

Asn Leu Trp Pro Thr Thr Ile Thr Phe Leu Thr Leu Phe Leu Leu Ser
    50                  55                  60

Leu Phe Tyr Ser Thr Ala Leu Thr Val Thr Ser Val Arg Gly Pro Ser
65                  70                  75                  80

Gly Asn Arg Glu Gly Pro Gln Tyr
                85
```

<210> SEQ ID NO 23

-continued

<211> LENGTH: 837
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

ctcaatcagc tttatgcaga gaagaagctt actgagctca ctgctggtgc tggtgtaggc 60

aagtgctgct ttggcaatct gggctgacct ggcttgtctc ctcagaactc cttctccaac 120

cctggagcag gcttccatgc tgctgtgggc gtccttgctg gcctttgctc cagtctgtgg 180

acaatctggc tcttgctctg ttgcagattg gcagatgccg cctccctatg tggtgctgga 240

cttgccgcag gagaccctgg aggaggagac ccccggcgcc aacctgtggc ccaccaccat 300

caccttcctc accctcttcc tgctgagcct gttctatagc acagcactga ccgtgaccag 360

cgtccggggc ccatctggca acagggaggg cccccagtac tgagcgggag ccggcaaggc 420

acaggtggga gcccaggagg gggatgagcc cacagtggat gaggtgggct gcagtgcttg 480

gctaagagga gagcaccacc tgctcccact gtgggggggac gtgctctcct ggggggccct 540

tcacagacac tgaggacacg cgcaggccca gggtcagggc tgagcttccc tccagtgcag 600

taacgaggat tccgtccagg ctcccatgag caggccaggg ctgagacaga gggcgttggc 660

aaggatgctg ctcttcaggc tgtgacccct ctgtctttgc agggaggaag tgtggaggaa 720

cctcttggag aagccagcta tgcttgccag aactcagccc tttcagacgt caccgacccg 780

cccttactca catgccttcc aggtgcaata aagtggcccc aaggaaaaaa aaaaaaa 837

<210> SEQ ID NO 24
<211> LENGTH: 90
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

tcccactgac gcatgcagga aggggcacct ccccttaacc acactgctct gtacggggca 60

cgtgggcaca ggtgcacact cacactcaca 90

<210> SEQ ID NO 25
<211> LENGTH: 89
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

ggcctgacag caacttttct tctactagtt catcttaaca cactgctctg tacggggcac 60

gtgggcacag gtgcacactc acactcaca 89

<210> SEQ ID NO 26
<211> LENGTH: 89
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

ggcctgacag caacttttct tctactagtt catcttaact ttatcctggt aactggcgag 60

acaacctgtc ttaagtaact gaagggaaa 89

<210> SEQ ID NO 27
<211> LENGTH: 77
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

tcccactgac gcaggaagga tcttaagttt atcctggtaa ctggcgagac aacctgtctt 60

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aagtaactga agggaaa 77

<210> SEQ ID NO 28
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Met Ala Met Glu Thr Gln Met Ser Gln Asn Val Cys Pro Arg Asn Leu
1 5 10 15

Trp Leu Leu Gln Pro Leu Thr Val Leu Leu Leu Leu Ala Ser Ala Asp
20 25 30

Ser Gln Ala Ala Ala Pro Pro Lys Ala Val Leu Lys Leu Glu Pro Pro
35 40 45

Trp Ile Asn Val Leu Gln Glu Asp Ser Val Thr Leu Thr Cys Cys Gly
50 55 60

Ala Arg Ser Pro Glu Ser Pro Ser Ile Gln Trp Phe His His Asn Gly
65 70 75 80

Asn Leu Ile Pro Ile His Thr Gln Ser Ser Tyr Arg Phe Lys Ala Asn
85 90 95

Asn Asn Asp Ser Gly Glu Tyr Thr Cys Gln Thr Gly Gln Thr Ser Leu
100 105 110

Ser Asp Pro Val His Leu Thr Val Leu Ser Glu Trp Leu Leu Leu Gln
115 120 125

Thr Pro His Leu Glu Phe Gln Glu Gly Glu Thr Ile Asn Leu Arg Cys
130 135 140

His Ser Trp Lys Asp Lys Pro Leu Val Lys Val Thr Glu Glu Gln Asn
145 150 155 160

Gly Lys Ser Gln Lys Phe Ser Arg Leu Asp Pro Thr Phe Ser Ile Pro
165 170 175

Gln Ala Asn His Ser His Ser Gly Asp Tyr His Cys Thr Gly Asn Cys
180 185 190

Gly Tyr Thr Leu Phe Ser Ser Lys
195 200

<210> SEQ ID NO 29
<211> LENGTH: 184
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Met Trp Gln Leu Leu Leu Pro Thr Ala Leu Leu Leu Leu Val Ser Ala
1 5 10 15

Gly Met Arg Thr Glu Asp Leu Pro Lys Ala Val Val Phe Leu Glu Pro
20 25 30

Gln Trp Tyr Arg Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Cys
35 40 45

Gly Ala Tyr Ser Pro Glu Leu Asn Ser Thr Gln Trp Phe His Asn Glu
50 55 60

Ser Leu Ile Ser Glu Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
65 70 75 80

Val Asp Asp Ser Gly Glu Tyr Arg Cys Gln Thr Asn Leu Ser Thr Leu
85 90 95

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
100 105 110

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Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
        115                 120                 125

His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
    130                 135                 140

Gly Lys Gly Arg Lys Tyr Phe His His Asn Ser Asp Phe Tyr Ile Pro
145                 150                 155                 160

Gln Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Phe
                165                 170                 175

Gly Ser Lys Asn Val Ser Ser Glu
            180


<210> SEQ ID NO 30
<211> LENGTH: 188
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1               5                   10                  15

Phe Phe Ala Asp Asp Gly Val Leu Ala Val Pro Gln Lys Pro Lys Val
            20                  25                  30

Ser Leu Asn Pro Pro Trp Asn Arg Ile Phe Lys Gly Glu Asn Val Thr
        35                  40                  45

Leu Thr Cys Asn Gly Asn Asn Phe Phe Glu Val Ser Ser Thr Lys Trp
    50                  55                  60

Phe His Asn Gly Ser Leu Ser Glu Ser Thr Asn Ser Ser Leu Asn Ile
65                  70                  75                  80

Val Asn Ala Lys Phe Glu Asp Ser Gly Glu Tyr Lys Cys Gln His Gln
                85                  90                  95

Gln Val Asn Glu Ser Glu Pro Val Tyr Leu Glu Val Phe Ser Asp Trp
            100                 105                 110

Leu Leu Leu Gln Ala Ser Ala Glu Val Val Met Glu Gly Gln Pro Leu
        115                 120                 125

Phe Leu Arg Cys His Gly Trp Arg Asn Trp Pro Val Tyr Lys Val Ile
    130                 135                 140

Tyr Tyr Lys Asp Gly Glu Ala Leu Lys Tyr Trp Tyr Glu Asn His Asn
145                 150                 155                 160

Ile Ser Ile Thr Asn Ala Thr Val Glu Asp Ser Gly Thr Tyr Tyr Cys
                165                 170                 175

Thr Gly Lys Val Trp Gln Leu Asp Tyr Glu Ser Glu
            180                 185


<210> SEQ ID NO 31
<211> LENGTH: 378
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Met Trp Phe Leu Thr Thr Leu Leu Leu Trp Val Pro Val Asp Gly Gln
1               5                   10                  15

Val Asp Thr Thr Lys Ala Val Ile Ser Leu Gln Pro Pro Trp Val Ser
            20                  25                  30

Phe Val Gln Glu Glu Thr Val Thr Leu His Cys Glu Val Leu His Leu
        35                  40                  45

Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala Thr Gln
    50                  55                  60
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Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala Ser Val Asn Asp Ser
65                  70                  75                  80

Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp Pro Thr
                85                  90                  95

Trp Leu Glu Thr His Arg Gly Trp Leu Leu Leu Gln Tyr Ser Ser Arg
            100                 105                 110

Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg Cys His Ala Trp Lys
        115                 120                 125

Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys Ala Phe
    130                 135                 140

Lys Phe Phe His Trp Asn Ser Asn Leu Ile Ile Leu Lys Ile Asn Ile
145                 150                 155                 160

Ser Ser His Asn Gly Thr Tyr His Cys Ser Gly Asn Gly Lys His Arg
                165                 170                 175

Tyr Thr Ser Ala Gly Lys His Arg Tyr Thr Ser Ala Gly Ile Ser Val
            180                 185                 190

Thr Val Lys Glu Leu Phe Pro Ala Pro Val Leu Asn Ala Ser Val Thr
        195                 200                 205

Ser Pro Leu Leu Glu Gly Asn Leu Val Thr Leu Ser Cys Glu Thr Lys
    210                 215                 220

Leu Leu Leu Gln Arg Pro Gly Leu Gln Leu Tyr Phe Ser Phe Tyr Met
225                 230                 235                 240

Gly Ser Leu Thr Leu Arg Gly Arg Asn Thr Ser Ser Glu Tyr Gln Ile
                245                 250                 255

Leu Thr Ala Arg Arg Glu Asp Ser Gly Leu Tyr Trp Cys Glu Ala Ala
            260                 265                 270

Thr Glu Asp Gly Asn Val Leu Lys Arg Ser Pro Glu Leu Glu Leu Gln
        275                 280                 285

Val Leu Gly Leu Gln Leu Pro Thr Pro Val Val Trp Phe His Val Leu
    290                 295                 300

Gly Tyr Leu Ala Val Gly Ile Met Phe Leu Val Asn Thr Val Leu Trp
305                 310                 315                 320

Val Val Thr Ile Arg Lys Glu Leu Lys Arg Lys Lys Lys Trp Asp Leu
                325                 330                 335

Glu Ile Ser Leu Asp Ser Gly His Glu Lys Lys Val Thr Ser Ser Leu
            340                 345                 350

Gln Glu Asp Arg His Glu Glu Glu Glu Leu Lys Cys Gln Glu Gln Lys
        355                 360                 365

Gly Glu Gln Leu Gln Glu Gly Val His Arg
    370                 375


<210> SEQ ID NO 32
<211> LENGTH: 376
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Met Leu Leu Trp Ala Ser Leu Leu Ala Phe Ala Pro Val Cys Gly Gln
1               5                   10                  15

Ser Ala Ala Ala His Lys Pro Val Ile Ser Val His Pro Pro Trp Thr
            20                  25                  30

Thr Phe Phe Lys Gly Glu Arg Val Thr Leu Thr Cys Asn Gly Phe Gln
        35                  40                  45

Phe Tyr Ala Thr Glu Lys Thr Thr Trp Tyr His Arg His Tyr Trp Gly
    50                  55                  60
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Glu Lys Leu Thr Leu Thr Pro Gly Asn Thr Leu Glu Val Arg Ala Ser
65                  70                  75                  80

Gly Leu Tyr Arg Cys Gln Ala Arg Gly Ser Pro Arg Ser Asn Pro Val
                85                  90                  95

Arg Leu Leu Phe Ser Ser Asp Ser Leu Ile Leu Gln Ala Pro Tyr Ser
            100                 105                 110

Val Phe Glu Gly Asp Thr Leu Val Leu Arg Cys His Arg Arg Arg Lys
        115                 120                 125

Glu Lys Leu Thr Ala Val Lys Tyr Thr Trp Asn Gly Asn Ile Leu Ser
    130                 135                 140

Ile Ser Asn Lys Ser Trp Asp Leu Leu Ile Pro Gln Ala Ser Ser Asn
145                 150                 155                 160

Asn Asn Gly Asn Tyr Arg Cys Ile Gly Tyr Gly Val Glu Asn Asp Val
                165                 170                 175

Phe Arg Ser Asn Gly Asp Glu Asn Asp Val Phe Arg Ser Asn Phe Lys
            180                 185                 190

Ile Ile Lys Ile Gln Glu Leu Phe Pro His Pro Glu Leu Lys Ala Thr
        195                 200                 205

Asp Ser Gln Pro Thr Glu Gly Asn Ser Val Asn Leu Ser Cys Glu Thr
    210                 215                 220

Gln Leu Pro Pro Glu Arg Ser Asp Thr Pro Leu His Phe Asn Phe Phe
225                 230                 235                 240

Arg Asp Gly Glu Val Ile Leu Ser Asp Trp Ser Thr Tyr Pro Glu Leu
                245                 250                 255

Gln Leu Pro Thr Val Trp Arg Glu Asn Ser Gly Ser Tyr Trp Cys Gly
            260                 265                 270

Ala Glu Thr Val Arg Gly Asn Ile His Lys His Ser Pro Ser Leu Gln
        275                 280                 285

Ile His Val Gln Arg Ile Pro Val Ser Gly Val Leu Leu Glu Thr Gln
    290                 295                 300

Pro Ser Gly Gly Gln Ala Val Glu Gln Glu Met Leu Val Leu Val Cys
305                 310                 315                 320

Ser Val Ala Glu Gly Thr Gly Asp Thr Thr Phe Ser Trp His Arg Glu
                325                 330                 335

Asp Met Gln Glu Ser Leu Gly Arg Lys Thr Gln Arg Ser Leu Arg Ala
            340                 345                 350

Glu Leu Glu Leu Pro Ala Ile Arg Gln Ser His Ala Gly Gly Tyr Tyr
        355                 360                 365

Cys Thr Ala Asp Asn Ser Tyr Gly
    370                 375


<210> SEQ ID NO 33
<211> LENGTH: 373
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Met Leu Leu Trp Val Ile Leu Leu Val Leu Ala Pro Val Ser Gly Gln
1               5                   10                  15

Phe Ala Arg Thr Pro Arg Pro Ile Ile Phe Leu Gln Pro Pro Trp Thr
            20                  25                  30

Thr Val Phe Gln Gly Glu Arg Val Thr Leu Thr Cys Lys Gly Phe Arg
        35                  40                  45

Phe Tyr Ser Pro Gln Arg Thr Arg Trp Tyr His Arg Tyr Leu Gly Lys
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    50                  55                  60

Glu Ile Leu Arg Glu Thr Pro Asp Asn Ile Leu Glu Val Gln Glu Ser
65                  70                  75                  80

Gly Glu Tyr Arg Cys Gln Ala Gln Gly Ser Pro Leu Ser Ser Pro Val
                85                  90                  95

His Leu Asp Phe Ser Ser Ala Ser Leu Ile Leu Gln Ala Pro Leu Ser
            100                 105                 110

Val Phe Glu Gly Asp Ser Val Val Leu Arg Cys Arg Ala Lys Ala Glu
        115                 120                 125

Val Thr Leu Asn Asn Thr Ile Tyr Lys Asn Asp Asn Val Leu Ala Phe
    130                 135                 140

Leu Asn Lys Arg Thr Asp Phe His Ile Pro His Ala Cys Leu Lys Asp
145                 150                 155                 160

Asn Gly Ala Tyr Arg Cys Thr Gly Tyr Lys Glu Ser Cys Cys Pro Val
                165                 170                 175

Ser Ser Asn Lys Glu Ser Cys Cys Pro Val Ser Ser Asn Thr Val Lys
            180                 185                 190

Ile Gln Val Gln Glu Pro Phe Thr Arg Pro Val Leu Arg Ala Ser Ser
        195                 200                 205

Phe Gln Pro Thr Ser Gly Asn Pro Val Thr Leu Thr Cys Glu Thr Gln
    210                 215                 220

Leu Ser Leu Glu Arg Ser Asp Val Pro Leu Arg Phe Arg Phe Phe Arg
225                 230                 235                 240

Asp Asp Gln Thr Leu Gly Leu Gly Trp Ser Leu Ser Pro Asn Phe Gln
                245                 250                 255

Ile Thr Ala Met Trp Ser Lys Asp Ser Gly Phe Tyr Trp Cys Lys Ala
            260                 265                 270

Ala Thr Met Pro His Ser Val Ile Ser Asp Ser Pro Arg Ser Trp Ile
        275                 280                 285

Gln Val Gln Ile Pro Ala Ser His Pro Val Leu Thr Leu Ser Pro Glu
    290                 295                 300

Lys Ala Leu Asn Phe Glu Gly Thr Lys Val Thr Leu His Cys Glu Thr
305                 310                 315                 320

Gln Glu Asp Ser Leu Arg Thr Leu Tyr Arg Phe Tyr His Glu Gly Val
                325                 330                 335

Pro Leu Arg His Lys Ser Val Arg Cys Glu Arg Gly Ala Ser Ile Ser
            340                 345                 350

Phe Ser Leu Thr Thr Glu Asn Ser Gly Asn Tyr Tyr Cys Thr Ala Asp
        355                 360                 365

Asn Gly Leu Gly Ala
    370


<210> SEQ ID NO 34
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa = D or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(8)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa = D or E
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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(11)
<223> OTHER INFORMATION: Xaa = Any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (13)..(14)
<223> OTHER INFORMATION: Xaa = Any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa = I or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (16)..(22)
<223> OTHER INFORMATION: Xaa = Any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (24)..(25)
<223> OTHER INFORMATION: Xaa = Any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: Xaa = I or L

<400> SEQUENCE: 34

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Tyr Xaa Xaa Xaa
20 25

<210> SEQ ID NO 35
<211> LENGTH: 63
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Glu Ser Ser His Ser Ile Cys Pro Ala Gln Val Glu Leu Gln Ser Leu
1 5 10 15

Tyr Val Asp Val His Pro Lys Lys Gly Asp Leu Val Tyr Ser Glu Ile
20 25 30

Gln Thr Thr Thr Leu Gly Glu Glu Glu Glu Glu Ala Asn Thr Ser Arg
35 40 45

Thr Leu Leu Glu Asp Lys Asp Val Ser Val Val Tyr Ser Glu Val
50 55 60

<210> SEQ ID NO 36
<211> LENGTH: 39
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Asp Asn Lys Glu Pro Leu Asn Ser Asp Val Gln Tyr Thr Glu Val Gln
1 5 10 15

Val Ser Ser Ala Glu Trp Ser His Lys Asp Leu Gly Lys Lys Asp Thr
20 25 30

Glu Thr Val Tyr Ser Glu Val
35

<210> SEQ ID NO 37
<211> LENGTH: 68
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (38)..(61)
<223> OTHER INFORMATION: Xaa = any amino acid

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<400> SEQUENCE: 37

Asp Ser Asp Ser Gln Glu Pro Thr Tyr His Asn Val Pro Ala Trp Glu
1 5 10 15

Glu Leu Gln Pro Val Tyr Thr Asn Ala Asn Pro Arg Gly Glu Asn Val
20 25 30

Val Tyr Ser Glu Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ile Tyr
50 55 60

Ser Glu Val Lys
65

<210> SEQ ID NO 38
<211> LENGTH: 65
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (38)..(58)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 38

Ala Ser Asp Gln Arg Asp Leu Thr Glu His Lys Pro Ser Val Ser Asn
1 5 10 15

His Thr Gln Asp His Ser Asn Asp Pro Pro Asn Lys Met Asn Glu Val
20 25 30

Thr Tyr Ser Thr Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ile Tyr Ser Glu Val
50 55 60

Lys
65

<210> SEQ ID NO 39
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Immune-receptor Tyrosine-based Inhibition Motif
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa = S, V, L or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa = L or V

<400> SEQUENCE: 39

Xaa Xaa Tyr Xaa Xaa Xaa
1 5

<210> SEQ ID NO 40
<211> LENGTH: 5321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 40

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ctggctcctg tcagtggaca gtttgcaagg acacccaggc ccattatttt cctccagcct 180

ccatggacca cagtcttcca aggagagaga gtgaccctca cttgcaaggg atttcgcttc 240

tactcaccac agaaaacaaa atggtaccat cggtaccttg ggaaagaaat actaagagaa 300

accccagaca atatccttga ggttcaggaa tctggagagt acagatgcca ggcccagggc 360

tcccctctca gtagccctgt gcacttggat ttttcttcag cttcgctgat cctgcaagct 420

ccactttctg tgtttgaagg agactctgtg gttctgaggt gccgggcaaa ggcggaagta 480

acactgaata atactattta caagaatgat aatgtcctgg cattccttaa taaaagaact 540

gacttccata ttcctcatgc atgtctcaag gacaatggtg catatcgctg tactggatat 600

aaggaaagtt gttgccctgt ttcttccaat acagtcaaaa tccaagtcca agagccattt 660

acacgtccag tgctgagagc cagctccttc cagcccatca gcgggaaccc agtgaccctg 720

acctgtgaga cccagctctc tctagagagg tcagatgtcc cgctccggtt ccgcttcttc 780

agagatgacc agaccctggg attaggctgg agtctctccc cgaatttcca gattactgcc 840

atgtggagta aagattcagg gttctactgg tgtaaggcag caacaatgcc tcacagcgtc 900

atatctgaca gcccgagatc ctggatacag gtgcagatcc ctgcatctca tcctgtcctc 960

actctcagcc ctgaaaaggc tctgaatttt gagggaacca aggtgacact tcactgtgaa 1020

acccaggaag attctctgcg cactttgtac aggttttatc atgagggtgt ccccctgagg 1080

cacaagtcag tccgctgtga aaggggagca tccatcagct tctcactgac tacagagaat 1140

tcagggaact actactgcac agctgacaat ggccttggcg ccaagcccag taaggctgtg 1200

agcctctcag tcactgttcc cgtgtctcat cctgtcctca acctcagctc tcctgaggac 1260

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ggaggagtgg ccatcagctt ctctctgact gcagagcatt cagggaacta ctactgcaca 1440

gctgacaatg gctttggccc ccagcgcagt aaggcggtga gcctctccat cactgtccct 1500

gtgtctcatc ctgtcctcac cctcagctct gctgaggccc tgacttttga aggagccact 1560

gtgacacttc actgtgaagt ccagagaggt tccccacaaa tcctatacca gttttatcat 1620

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tctctgactg aaggacattc agggaattac tactgcacag ctgacaatgg ctttggtccc 1740

cagcgcagtg aagtggtgag ccttttttgtc actgttccag tgtctcgccc catcctcacc 1800

ctcagggttc ccagggccca ggctgtggtg ggggacctgc tggagcttca ctgtgaggcc 1860

ccgagaggct ctcccccaat cctgtactgg ttttatcatg aggatgtcac cctggggagc 1920

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ggaaactact catgtgaggc caacaatggc ctagtggccc agcacagtga cacaatatca 2040

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gacaatggtc tggaggccca gcgcagtgag atggtgacac tgaaagttgc agttccggtg 2340

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gagcttcact gtgaggccct gagaggctct cccctgatcc tgtaccggtt ttttcatgag 2460

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acaggagtcg ccgggggcct gctcagcata gcaggccttg ctgcgggggc actgctgctc 2700

tactgctggc tctcgagaaa agcagggaga aagcctgcct ctgaccccgc caggagccct 2760

tcagactcgg actcccaaga gcccacctat cacaatgtac cagcctggga agagctgcaa 2820

ccagtgtaca ctaatgcaaa tcctagagga gaaaatgtgg tttactcaga agtacggatc 2880

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tcccctatca tctactctga agttaaggtg gcgtcaaccc cggtttccgg atccctgttc 3000

ttggcttcct cagctcctca cagatgagtc cacacgtctc tccaactgct gtttcagcct 3060

ctgcacccca aagttcccct tgggggagaa gcagcattga agtgggaaga tttaggctgc 3120

cccagaccat atctactggc ctttgtttca catgtcctca ttctcagtct gaccagaatg 3180

cagggccctg ctggactgtc acctgtttcc cagttaaagc cctgactggc aggtttttta 3240

atccagtggc aaggtgctcc cactccaggg cccagcacat ctcctggatt ccttagtggg 3300

cttcagctgt ggttgctgtt ctgagtactg ctctcatcac acccccacag aggggtctt 3360

accacacaaa gggagagtgg gccttcagga gatgccgggc tggcctaaca gctcaggtgc 3420

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ccaagtaagt ggctttcata caccaagtcc cgaagttctt cccatcctaa cagaagtaac 3720

ccagcaagtc aaggccagga ggaccagggg tgcagacaga acacatactg gaacacagga 3780

ggtgctcaat tactatttga ctgactgact gaatgaatga atgaatgagg aagaaaactg 3840

tgggtaatca aactggcata aaatccagtg cactccctag gaaatccggg aggtattctg 3900

gcttcctaag aaacaacgga agagaaggag cttggatgaa gaaactgttc agcaagaaga 3960

agggcttctt cacactttta tgtgcttgtg gatcacctga ggatctgtga aaatacagat 4020

actgattcag tgggtctgtg tagagcctga gactgccatt ctaacatgtt cccaggggat 4080

gctgatgctg ctggccctgg gactgcactg catgcatgtg aagccctata ggtctcagca 4140

gaggcccatg gagagggaat gtgtggctct ggctgcccag ggcccaactc ggttcacacg 4200

gatcgtgctg ctccctggcc agcctttggc cacagcacca ccagctgctg ttgctgagag 4260

agcttcttct ctgtgacatg ttggctttca tcagccaccc tgggaagcgg aaagtagctg 4320

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gtgatgactt ttaagcccca cggccctgaa ataaaatcct tccaagggca ttggaagctc 4560

actccacctg aaccatggct tttcatgctt ccaagtgtca gggccttgcc cagatagaca 4620

gggctgactc tgctgcccca acctttcaag gaggaaacca gacacctgag acaggagcct 4680

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gtatgcagcc cagtgcagcc ttgcagagga caaggctgga ggcatttgtc atcactacag 4740

atatgcaact aaaatagacg tggagcaaga gaaatgcatt cccaccgagg ccgctttttt 4800

aggcctagtt gaaagtcaag aaggacagca gcaagcatag gctcaggatt aaagaaaaaa 4860

atctgctcac agtctgttct ggaggtcaca tcaccaacaa agctcacgcc ctatgcagtt 4920

ctgagaaggt ggaggcacca ggctcaaaag aggaaattta gaatttctca ttgggagagt 4980

aaggtacccc catcccagaa tgataactgc acagtggcag aacaaactcc accctaatgt 5040

gggtggaccc catccagtct gttgaaggcc tgaatgtaac aaaagggctt attcttcctc 5100

aagtaagggg gaactcctgc tttgggctgg gacataagtt tttctgcttt cagacgcaaa 5160

ctgaaaaatg gctcttcttg ggtcttgagc ttgctggcat atggactgaa agaaactatg 5220

ctattggatc tcctggatct ccagcttgct gactgcagat cttgagatat gtcagcctct 5280

acagtcacaa gagctaattc attctaataa accaatcttt c 5321

<210> SEQ ID NO 41
<211> LENGTH: 977
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Met Leu Leu Trp Val Ile Leu Leu Val Leu Ala Pro Val Ser Gly Gln
1 5 10 15

Phe Ala Arg Thr Pro Arg Pro Ile Ile Phe Leu Gln Pro Pro Trp Thr
20 25 30

Thr Val Phe Gln Gly Glu Arg Val Thr Leu Thr Cys Lys Gly Phe Arg
35 40 45

Phe Tyr Ser Pro Gln Lys Thr Lys Trp Tyr His Arg Tyr Leu Gly Lys
50 55 60

Glu Ile Leu Arg Glu Thr Pro Asp Asn Ile Leu Glu Val Gln Glu Ser
65 70 75 80

Gly Glu Tyr Arg Cys Gln Ala Gln Gly Ser Pro Leu Ser Ser Pro Val
85 90 95

His Leu Asp Phe Ser Ser Ala Ser Leu Ile Leu Gln Ala Pro Leu Ser
100 105 110

Val Phe Glu Gly Asp Ser Val Val Leu Arg Cys Arg Ala Lys Ala Glu
115 120 125

Val Thr Leu Asn Asn Thr Ile Tyr Lys Asn Asp Asn Val Leu Ala Phe
130 135 140

Leu Asn Lys Arg Thr Asp Phe His Ile Pro His Ala Cys Leu Lys Asp
145 150 155 160

Asn Gly Ala Tyr Arg Cys Thr Gly Tyr Lys Glu Ser Cys Cys Pro Val
165 170 175

Ser Ser Asn Thr Val Lys Ile Gln Val Gln Glu Pro Phe Thr Arg Pro
180 185 190

Val Leu Arg Ala Ser Ser Phe Gln Pro Ile Ser Gly Asn Pro Val Thr
195 200 205

Leu Thr Cys Glu Thr Gln Leu Ser Leu Glu Arg Ser Asp Val Pro Leu
210 215 220

Arg Phe Arg Phe Phe Arg Asp Asp Gln Thr Leu Gly Leu Gly Trp Ser
225 230 235 240

Leu Ser Pro Asn Phe Gln Ile Thr Ala Met Trp Ser Lys Asp Ser Gly
245 250 255

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Phe Tyr Trp Cys Lys Ala Ala Thr Met Pro His Ser Val Ile Ser Asp
            260                 265                 270

Ser Pro Arg Ser Trp Ile Gln Val Gln Ile Pro Ala Ser His Pro Val
        275                 280                 285

Leu Thr Leu Ser Pro Glu Lys Ala Leu Asn Phe Glu Gly Thr Lys Val
    290                 295                 300

Thr Leu His Cys Glu Thr Gln Glu Asp Ser Leu Arg Thr Leu Tyr Arg
305                 310                 315                 320

Phe Tyr His Glu Gly Val Pro Leu Arg His Lys Ser Val Arg Cys Glu
                325                 330                 335

Arg Gly Ala Ser Ile Ser Phe Ser Leu Thr Thr Glu Asn Ser Gly Asn
            340                 345                 350

Tyr Tyr Cys Thr Ala Asp Asn Gly Leu Gly Ala Lys Pro Ser Lys Ala
        355                 360                 365

Val Ser Leu Ser Val Thr Val Pro Val Ser His Pro Val Leu Asn Leu
    370                 375                 380

Ser Ser Pro Glu Asp Leu Ile Phe Glu Gly Ala Lys Val Thr Leu His
385                 390                 395                 400

Cys Glu Ala Gln Arg Gly Ser Leu Pro Ile Leu Tyr Gln Phe His His
                405                 410                 415

Glu Asp Ala Ala Leu Glu Arg Arg Ser Ala Asn Ser Ala Gly Gly Val
            420                 425                 430

Ala Ile Ser Phe Ser Leu Thr Ala Glu His Ser Gly Asn Tyr Tyr Cys
        435                 440                 445

Thr Ala Asp Asn Gly Phe Gly Pro Gln Arg Ser Lys Ala Val Ser Leu
    450                 455                 460

Ser Ile Thr Val Pro Val Ser His Pro Val Leu Thr Leu Ser Ser Ala
465                 470                 475                 480

Glu Ala Leu Thr Phe Glu Gly Ala Thr Val Thr Leu His Cys Glu Val
                485                 490                 495

Gln Arg Gly Ser Pro Gln Ile Leu Tyr Gln Phe Tyr His Glu Asp Met
            500                 505                 510

Pro Leu Trp Ser Ser Ser Thr Pro Ser Val Gly Arg Val Ser Phe Ser
        515                 520                 525

Phe Ser Leu Thr Glu Gly His Ser Gly Asn Tyr Tyr Cys Thr Ala Asp
    530                 535                 540

Asn Gly Phe Gly Pro Gln Arg Ser Glu Val Val Ser Leu Phe Val Thr
545                 550                 555                 560

Val Pro Val Ser Arg Pro Ile Leu Thr Leu Arg Val Pro Arg Ala Gln
                565                 570                 575

Ala Val Val Gly Asp Leu Leu Glu Leu His Cys Glu Ala Pro Arg Gly
            580                 585                 590

Ser Pro Pro Ile Leu Tyr Trp Phe Tyr His Glu Asp Val Thr Leu Gly
        595                 600                 605

Ser Ser Ser Ala Pro Ser Gly Gly Glu Ala Ser Phe Asn Leu Ser Leu
    610                 615                 620

Thr Ala Glu His Ser Gly Asn Tyr Ser Cys Glu Ala Asn Asn Gly Leu
625                 630                 635                 640

Val Ala Gln His Ser Asp Thr Ile Ser Leu Ser Val Ile Val Pro Val
                645                 650                 655

Ser Arg Pro Ile Leu Thr Phe Arg Ala Pro Arg Ala Gln Ala Val Val
            660                 665                 670

Gly Asp Leu Leu Glu Leu His Cys Glu Ala Leu Arg Gly Ser Ser Pro
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        675                 680                 685

Ile Leu Tyr Trp Phe Tyr His Glu Asp Val Thr Leu Gly Lys Ile Ser
    690                 695                 700

Ala Pro Ser Gly Gly Gly Ala Ser Phe Asn Leu Ser Leu Thr Thr Glu
705                 710                 715                 720

His Ser Gly Ile Tyr Ser Cys Glu Ala Asp Asn Gly Leu Glu Ala Gln
                725                 730                 735

Arg Ser Glu Met Val Thr Leu Lys Val Ala Val Pro Val Ser Arg Pro
            740                 745                 750

Val Leu Thr Leu Arg Ala Pro Gly Thr His Ala Ala Val Gly Asp Leu
        755                 760                 765

Leu Glu Leu His Cys Glu Ala Leu Arg Gly Ser Pro Leu Ile Leu Tyr
    770                 775                 780

Arg Phe Phe His Glu Asp Val Thr Leu Gly Asn Arg Ser Ser Pro Ser
785                 790                 795                 800

Gly Gly Ala Ser Leu Asn Leu Ser Leu Thr Ala Glu His Ser Gly Asn
                805                 810                 815

Tyr Ser Cys Glu Ala Asp Asn Gly Leu Gly Ala Gln Arg Ser Glu Thr
            820                 825                 830

Val Thr Leu Tyr Ile Thr Gly Leu Thr Ala Asn Arg Ser Gly Pro Phe
        835                 840                 845

Ala Thr Gly Val Ala Gly Gly Leu Leu Ser Ile Ala Gly Leu Ala Ala
    850                 855                 860

Gly Ala Leu Leu Leu Tyr Cys Trp Leu Ser Arg Lys Ala Gly Arg Lys
865                 870                 875                 880

Pro Ala Ser Asp Pro Ala Arg Ser Pro Ser Asp Ser Asp Ser Gln Glu
                885                 890                 895

Pro Thr Tyr His Asn Val Pro Ala Trp Glu Glu Leu Gln Pro Val Tyr
            900                 905                 910

Thr Asn Ala Asn Pro Arg Gly Glu Asn Val Val Tyr Ser Glu Val Arg
        915                 920                 925

Ile Ile Gln Glu Lys Lys Lys His Ala Val Ala Ser Asp Pro Arg His
    930                 935                 940

Leu Arg Asn Lys Gly Ser Pro Ile Ile Tyr Ser Glu Val Lys Val Ala
945                 950                 955                 960

Ser Thr Pro Val Ser Gly Ser Leu Phe Leu Ala Ser Ser Ala Pro His
                965                 970                 975

Arg
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<210> SEQ ID NO 42
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

ggcacctccc cttaac 16

<210> SEQ ID NO 43
<211> LENGTH: 2797
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

gtgcagtgtc ctgactgtaa gatcaagtcc aaacctgttt tggaattgag gaaacttctc 60

ttttgatctc agcccttggt ggtccaggtc ttcatgctgc tgtgggtgat attactggtc 120

-continued

ctggctcctg tcagtggaca gtttgcaagg acacccaggc ccattatttt cctccagcct 180

ccatggacca cagtcttcca aggagagaga gtgaccctca cttgcaaggg atttcgcttc 240

tactcaccac agaaaacaaa atggtaccat cggtaccttg ggaaagaaat actaagagaa 300

accccagaca atatccttga ggttcaggaa tctggagagt acagatgcca ggcccagggc 360

tcccctctca gtagccctgt gcacttggat ttttcttcag cttcgctgat cctgcaagct 420

ccactttctg tgtttgaagg agactctgtg gttctgaggt gccgggcaaa ggcggaagta 480

acactgaata atactattta caagaatgat aatgtcctgg cattccttaa taaaagaact 540

gacttccata ttcctcatgc atgtctcaag gacaatggtg catatcgctg tactggatat 600

aaggaaagtt gttgccctgt ttcttccaat acagtcaaaa tccaagtcca agagccattt 660

acacgtccag tgctgagagc cagctccttc cagcccatca gcgggaaccc agtgaccctg 720

acctgtgaga cccagctctc tctagagagg tcagatgtcc cgctccggtt ccgcttcttc 780

agagatgacc agaccctggg attaggctgg agtctctccc cgaatttcca gattactgcc 840

atgtggagta aagattcagg gttctactgg tgtaaggcag caacaatgcc tcacagcgtc 900

atatctgaca gcccgagatc ctggatacag gtgcagatcc ctgcatctca tcctgtcctc 960

actctcagcc ctgaaaaggc tctgaatttt gagggaacca aggtgacact tcactgtgaa 1020

acccaggaag attctctgcg cactttgtac aggttttatc atgagggtgt ccccctgagg 1080

cacaagtcag tccgctgtga aaggggagca tccatcagct tctcactgac tacagagaat 1140

tcagggaact actactgcac agctgacaat ggccttggcg ccaagcccag taaggctgtg 1200

agcctctcag tcactgttcc cgtgtctcat cctgtcctca acctcagctc tcctgaggac 1260

ctgatttttg agggagccaa ggtgacactt cactgtgaag cccagagagg ttcactcccc 1320

atcctgtacc agtttcatca tgaggatgct gccctggagc gtaggtcggc caactctgca 1380

ggaggagtgg ccatcagctt ctctctgact gcagagcatt cagggaacta ctactgcaca 1440

gctgacaatg gctttggccc ccagcgcagt aaggcggtga gcctctccat cactgtccct 1500

gtgtctcatc ctgtcctcac cctcagctct gctgaggccc tgacttttga aggagccact 1560

gtgacacttc actgtgaagt ccagagaggt tccccacaaa tcctatacca gttttatcat 1620

gaggacatgc ccctgtggag cagctcaaca ccctctgtgg gaagagtgtc cttcagcttc 1680

tctctgactg aaggacattc agggaattac tactgcacag ctgacaatgg ctttggtccc 1740

cagcgcagtg aagtggtgag ccttttttgtc actgttccag tgtctcgccc catcctcacc 1800

ctcagggttc ccagggccca ggctgtggtg ggggacctgc tggagcttca ctgtgaggcc 1860

ccgagaggct ctcccccaat cctgtactgg ttttatcatg aggatgtcac cctggggagc 1920

agctcagccc cctctggagg agaagcttct ttcaacctct ctctgactgc agaacattct 1980

ggaaactact catgtgaggc caacaatggc ctagtggccc agcacagtga cacaatatca 2040

ctcagtgtta tagttccagt atctcgtccc atcctcacct tcagggctcc cagggcccag 2100

gctgtggtgg gggacctgct ggagcttcac tgtgaggccc tgagaggctc ctccccaatc 2160

ctgtactggt tttatcatga agatgtcacc ctgggtaaga tctcagcccc ctctggagga 2220

ggggcctcct tcaacctctc tctgactaca gaacattctg gaatctactc ctgtgaggca 2280

gacaatggtc tggaggccca gcgcagtgag atggtgacac tgaaagttgc aggtgagtgg 2340

gccctgccca ccagcagcac atctgagaac tgactgtgcc tgttctccct gcagctgaaa 2400

atggagccac agagctcctc agggctgttt gcttgtgtgg catcccagca cacttcctgc 2460

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ctgcagaacc tccctgtgaa agtctcggat cctttgtggt atggttccag gaatctgatg 2520

tttcccagca gtcttcttga agatgatcaa agcacctcac taaaaatgca aataagactt 2580

ttttagaaca taaactatat tctgaactga aattattaca tgaaaatgaa accaaagaat 2640

tctgagcata tgtttctctg ccgtagaaag gattaagctg tttcttgtcc ggattcttct 2700

ctcattgact tctaagaagc ctctactctt gagtctcttt cattactggg gatgtaaatg 2760

ttccttacat ttccacatta aaaatcctat gttaacg 2797

<210> SEQ ID NO 44
<211> LENGTH: 759
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Met Leu Leu Trp Val Ile Leu Leu Val Leu Ala Pro Val Ser Gly Gln
1 5 10 15

Phe Ala Arg Thr Pro Arg Pro Ile Ile Phe Leu Gln Pro Pro Trp Thr
20 25 30

Thr Val Phe Gln Gly Glu Arg Val Thr Leu Thr Cys Lys Gly Phe Arg
35 40 45

Phe Tyr Ser Pro Gln Lys Thr Lys Trp Tyr His Arg Tyr Leu Gly Lys
50 55 60

Glu Ile Leu Arg Glu Thr Pro Asp Asn Ile Leu Glu Val Gln Glu Ser
65 70 75 80

Gly Glu Tyr Arg Cys Gln Ala Gln Gly Ser Pro Leu Ser Ser Pro Val
85 90 95

His Leu Asp Phe Ser Ser Ala Ser Leu Ile Leu Gln Ala Pro Leu Ser
100 105 110

Val Phe Glu Gly Asp Ser Val Val Leu Arg Cys Arg Ala Lys Ala Glu
115 120 125

Val Thr Leu Asn Asn Thr Ile Tyr Lys Asn Asp Asn Val Leu Ala Phe
130 135 140

Leu Asn Lys Arg Thr Asp Phe His Ile Pro His Ala Cys Leu Lys Asp
145 150 155 160

Asn Gly Ala Tyr Arg Cys Thr Gly Tyr Lys Glu Ser Cys Cys Pro Val
165 170 175

Ser Ser Asn Thr Val Lys Ile Gln Val Gln Glu Pro Phe Thr Arg Pro
180 185 190

Val Leu Arg Ala Ser Ser Phe Gln Pro Ile Ser Gly Asn Pro Val Thr
195 200 205

Leu Thr Cys Glu Thr Gln Leu Ser Leu Glu Arg Ser Asp Val Pro Leu
210 215 220

Arg Phe Arg Phe Phe Arg Asp Asp Gln Thr Leu Gly Leu Gly Trp Ser
225 230 235 240

Leu Ser Pro Asn Phe Gln Ile Thr Ala Met Trp Ser Lys Asp Ser Gly
245 250 255

Phe Tyr Trp Cys Lys Ala Ala Thr Met Pro His Ser Val Ile Ser Asp
260 265 270

Ser Pro Arg Ser Trp Ile Gln Val Gln Ile Pro Ala Ser His Pro Val
275 280 285

Leu Thr Leu Ser Pro Glu Lys Ala Leu Asn Phe Glu Gly Thr Lys Val
290 295 300

Thr Leu His Cys Glu Thr Gln Glu Asp Ser Leu Arg Thr Leu Tyr Arg
305 310 315 320

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Phe Tyr His Glu Gly Val Pro Leu Arg His Lys Ser Val Arg Cys Glu
                325                 330                 335

Arg Gly Ala Ser Ile Ser Phe Ser Leu Thr Thr Glu Asn Ser Gly Asn
            340                 345                 350

Tyr Tyr Cys Thr Ala Asp Asn Gly Leu Gly Ala Lys Pro Ser Lys Ala
        355                 360                 365

Val Ser Leu Ser Val Thr Val Pro Val Ser His Pro Val Leu Asn Leu
    370                 375                 380

Ser Ser Pro Glu Asp Leu Ile Phe Glu Gly Ala Lys Val Thr Leu His
385                 390                 395                 400

Cys Glu Ala Gln Arg Gly Ser Leu Pro Ile Leu Tyr Gln Phe His His
                405                 410                 415

Glu Asp Ala Ala Leu Glu Arg Arg Ser Ala Asn Ser Ala Gly Gly Val
            420                 425                 430

Ala Ile Ser Phe Ser Leu Thr Ala Glu His Ser Gly Asn Tyr Tyr Cys
        435                 440                 445

Thr Ala Asp Asn Gly Phe Gly Pro Gln Arg Ser Lys Ala Val Ser Leu
    450                 455                 460

Ser Ile Thr Val Pro Val Ser His Pro Val Leu Thr Leu Ser Ser Ala
465                 470                 475                 480

Glu Ala Leu Thr Phe Glu Gly Ala Thr Val Thr Leu His Cys Glu Val
                485                 490                 495

Gln Arg Gly Ser Pro Gln Ile Leu Tyr Gln Phe Tyr His Glu Asp Met
            500                 505                 510

Pro Leu Trp Ser Ser Ser Thr Pro Ser Val Gly Arg Val Ser Phe Ser
        515                 520                 525

Phe Ser Leu Thr Glu Gly His Ser Gly Asn Tyr Tyr Cys Thr Ala Asp
    530                 535                 540

Asn Gly Phe Gly Pro Gln Arg Ser Glu Val Val Ser Leu Phe Val Thr
545                 550                 555                 560

Val Pro Val Ser Arg Pro Ile Leu Thr Leu Arg Val Pro Arg Ala Gln
                565                 570                 575

Ala Val Val Gly Asp Leu Leu Glu Leu His Cys Glu Ala Pro Arg Gly
            580                 585                 590

Ser Pro Pro Ile Leu Tyr Trp Phe Tyr His Glu Asp Val Thr Leu Gly
        595                 600                 605

Ser Ser Ser Ala Pro Ser Gly Gly Glu Ala Ser Phe Asn Leu Ser Leu
    610                 615                 620

Thr Ala Glu His Ser Gly Asn Tyr Ser Cys Glu Ala Asn Asn Gly Leu
625                 630                 635                 640

Val Ala Gln His Ser Asp Thr Ile Ser Leu Ser Val Ile Val Pro Val
                645                 650                 655

Ser Arg Pro Ile Leu Thr Phe Arg Ala Pro Arg Ala Gln Ala Val Val
            660                 665                 670

Gly Asp Leu Leu Glu Leu His Cys Glu Ala Leu Arg Gly Ser Ser Pro
        675                 680                 685

Ile Leu Tyr Trp Phe Tyr His Glu Asp Val Thr Leu Gly Lys Ile Ser
    690                 695                 700

Ala Pro Ser Gly Gly Gly Ala Ser Phe Asn Leu Ser Leu Thr Thr Glu
705                 710                 715                 720

His Ser Gly Ile Tyr Ser Cys Glu Ala Asp Asn Gly Leu Glu Ala Gln
                725                 730                 735
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Arg Ser Glu Met Val Thr Leu Lys Val Ala Gly Glu Trp Ala Leu Pro
            740                 745                 750

Thr Ser Ser Thr Ser Glu Asn
        755
```

What is claimed is:

1. An isolated antibody which specifically binds to the extracellular domain of a human IRTA4 protein, wherein the amino acid sequence of the human IRTA4 protein is set forth in SEQ ID NO: 7.

2. The antibody of claim **1**, wherein the antibody is a monoclonal antibody.

3. The antibody of claim **2**, wherein the antibody is a humanized antibody.

4. The antibody of claim **1**, wherein the human IRTA4 protein is expressed on the surface of a cancer cell.

5. The antibody of claim **4**, wherein the antibody is a monoclonal antibody.

6. A composition comprising an amount of the antibody of any of claim **1**-**3**, **4** or **5** effective to bind cancer cells expressing IRTA4 so as to prevent growth of the cancer cells, and a pharmaceutically acceptable carrier.

7. An antibody which specifically binds to the extracellular domain of a human IRTA4 protein conjugated to a therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a radioisotope, a toxin, a toxoid or a chemotherapeutic agent; and wherein the amino acid sequence of the purified human IRTA4 protein is set forth in SEQ ID NO:7.

8. The antibody of claim **7**, wherein the human IRTA4 protein is expressed on the surface of a cancer cell.

9. The antibody of claim **7**, wherein the antibody is a monoclonal antibody.

10. The antibody of claim **9**, wherein the antibody is a humanized antibody.

11. The antibody of claim **8**, wherein the antibody is a monoclonal antibody.

12. A composition comprising an amount of the antibody of any of claim **7**, **8**-**9** or **10** or **11** effective to bind cancer cells expressing IRTA4 so as to prevent growth of the cancer cells, and a pharmaceutically acceptable carrier.

13. A composition comprising an amount of an antibody which binds to a human IRTA protein effective to bind cancer cells expressing IRTA4 so as to prevent growth of the cancer cells, and a pharmaceutically acceptable carrier, wherein the amino acid sequence of the human IRTA4 protein is set forth in SEQ ID NO:7.

14. The composition of claim **13**, wherein the antibody is a monoclonal antibody.

15. The composition of claim **14**, wherein the antibody is a humanized antibody.

16. A composition comprising a pharmaceutically acceptable carrier and an antibody which binds to a human IRTA4 protein conjugated to a therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a radioisotope, a toxin, a toxoid or a chemotherapeutic agent; wherein the amino acid sequence of the purified human IRTA4 protein is set forth in SEQ ID NO:7; and wherein the antibody conjugated to the therapeutic agent is present in an amount effective to bind cancer cells expressing IRTA4 so as to prevent growth of the cancer cells.

* * * * *